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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: FEBRUARY 1 2006

SUBJECT: Petition Number: 2E6490 – **Human Health Risk Assessment for Fipronil** - Incorporating the IR-4 Section 3 Petition for Registration on Onion and Shallot Seed (dry bulb) and a Proposed Permanent Tolerance on Potatoes and Sweet Potatoes.

DP Barcode:	D324269	Decision #:	305595
PC Code:	129121	Class:	Insecticide
Trade Name:	Regent® 4 SC Insecticide	EPA Reg. No.:	7969-207

TO: Dan Rosenblatt, Branch Chief
MUIER Branch
Registration Division (7505C)

FROM: Breann Hanson, ARIA Team
Technical Review Branch
Registration Division(RD) (7505C)

THRU: William Cutchin, ARIA Team
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Registration Division(RD) (7505C)

AND

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RAB1/HED (7509C)

BASF Corporation (formerly Rhône-Poulenc) has revised the proposed permanent tolerance for foliar applications of the insecticide fipronil, [5-amino-1-(2,6-dichloro-4-(trifluoromethyl) phenyl)-4-((1,R,S)-trifluoromethyl)sulfinyl)-1-H-pyrazole-3-carbonitrile] and its 2 metabolites MB45950 (5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)thio]-1H-pyrazole-3-carbonitrile) and MB46136 (5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile) and photodegradate MB46513 (5-amino-

1-(2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)]-1H-pyrazole-3-carbonitrile) to potato using in-furrow applications using Regent® 4 SC Insecticide to the tuberous and corm vegetables crop subgroup 1C and to propose a tolerance for potato wet peel. The registration applications for Agenda 1.67 SC insecticide (EPA Reg. No. 7969-ERT) and Agenda 80WG (EPA Reg. No. 7969-ERA) originally submitted to support the foliar use on potato are being withdrawn. BASF also indicated its intent to continue to support the proposed tolerances for wheat commodities to support proposed reduced replant intervals for inadvertant residues on wheat. In addition, the Interregional Research Project Number 4 (IR-4) has also submitted a petition for a Section 3 registration for application of fipronil to dry bulb onions as a seed treatment.

This risk assessment incorporates all current, pending, and proposed tolerances for fipronil as of January 19, 2005.

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1.0. EXECUTIVE SUMMARY

General Background

There are existing permanent tolerances (40 CFR §180.517(a)) for fipronil (+ its 2 metabolites and 1 photodegradate) in/on rice grain (0.04 ppm); rice straw (0.10 ppm); corn, field, grain (0.02 ppm); corn, field, stover (0.30 ppm); corn, field, forage (0.15 ppm); eggs (0.03 ppm); fat of cattle, goat, horse, and sheep (0.40 ppm); hog fat (0.04 ppm); hog liver (0.02 ppm); hog meat (0.01 ppm); hog meat byproducts (except liver) (0.01 ppm); liver of cattle, goat, horse, and sheep (0.10 ppm); meat byproducts of cattle, goat, horse, and sheep (except liver) (0.04 ppm); meat of cattle, goat, horse, and sheep (0.04 ppm); milk, fat (reflecting 0.05 ppm in whole milk) (1.50 ppm); poultry fat (0.05 ppm); poultry meat (0.02 ppm); and poultry meat byproducts (0.02 ppm). Recent tolerances for residues have been added for turnip (1.0 ppm) and rutabaga (1.0 ppm).

Tolerances are proposed for the combined residues of fipronil and its metabolites and photodegradate in or on the following raw agricultural commodities (RACs):

Vegetable, tuberous + corm, subgroup 1C	0.04 ppm
Potato wet peel	0.40 ppm
Wheat, grain [a]	0.04 ppm
Wheat, forage [a]	0.04 ppm
Wheat, hay [a]	0.04 ppm
Wheat, straw [a]	0.04 ppm
Onion (dry bulb), garlic, shallot (dry bulb)	0.02 ppm

[a] *Note to RD: There are no proposed uses for fipronil on wheat. The proposed tolerances for wheat RAC's are for inadvertent residues resulting from uptake by rotational crops. Tolerances for wheat commodities should be established under 40 CFR §180.517(d).*

The use of fipronil in/on cotton has been withdrawn by the registrant and so for the purpose of the dietary analysis the tolerance for cotton has been removed. Fipronil is not registered for use on rice in the United States; rice tolerances are established to cover residues on imported commodities.

There are registered residential uses (pet and termiticide uses and fire ant control) for fipronil.

The most recent human health risk assessment for fipronil was conducted in conjunction with a Section 18 request for the use of rutabaga and turnip in Oregon and its renewed registration for use on corn. (PP# 05OR18, DP Barcode: D316795, B. Hanson, 11/15/2005).

Hazard Assessment

Fipronil is a broad-spectrum insecticide belonging to the pyrazole class of insecticides. The toxicology database provides evidence of neurotoxic activity as evidenced by neurologic signs in several studies and species. Fipronil is also associated with alterations in the thyroid-pituitary hormonal status, resulting in alterations in thyroid hormonal levels and thyroid follicular cell tumors.

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical per 40 CFR Part 158 for fipronil and the hazard endpoints have been identified. However, the Hazard Identification Assessment Review Committee (HIARC) has requested a 28-day inhalation toxicity study in the rat. This study was requested to further characterize the inhalation hazard for use in the risk assessment of fipronil. There is high confidence in the quality of the existing studies and the reliability of the toxicity endpoints identified for use in risk assessment.

In acute toxicity studies, fipronil exhibits low to moderate toxicity, depending on the route of exposure and species. Fipronil has moderate acute toxicity (toxicity category II) by the oral and inhalation routes in rats. By the dermal route, it is of moderate toxicity in rabbits, and low toxicity in rats (III). Fipronil technical is relatively non-irritating to the skin (IV) and eye (III) of rabbits and is not a dermal sensitizer. Dermal absorption in rats is estimated to be 1% or less based on a dermal absorption study.

Fipronil is neurotoxic in both rats and dogs as evidenced by signs in the acute and subchronic screening batteries in the rat, in developmental neurotoxicity and chronic carcinogenicity studies in the rat, and in two chronic dog studies. Clinical signs of neurotoxicity were not observed in the mouse or rat at 28 or 90 days. The rat and mouse showed evidence of liver and/or thyroid alterations at all time periods (chronic only for the mouse).

There are no data gaps for the assessment of the effects of fipronil on developing animals following *in utero* and/or early postnatal exposure. This conclusion is based on the following acceptable studies: two-generation reproduction study in rats and prenatal developmental toxicity studies in rats and rabbits. In addition, an acceptable developmental neurotoxicity study was conducted with fipronil and reviewed by HED. Although there is no evidence of potential for enhanced pre- or post-natal susceptibility in infants and children in the developmental and reproduction studies, the developmental neurotoxicity study identified a developmental no observed adverse effect level (NOAEL) which was less than the maternal NOAEL indicating an apparent susceptibility issue. However, the HIARC concluded that the apparent increased susceptibility in the developmental neurotoxicity study was not supported by the overall weight-of-the-evidence. The Food Quality Protection Act Safety Factor Committee (FQPA SFC)

recommended that the 10x factor for enhanced sensitivity to infants and children (as required by FQPA) should be **reduced to 1x** for fipronil.

The fipronil photodegradate MB46513, is not an animal metabolite. However, significant quantities are produced in certain crops (*e.g.*, rice). Therefore, it was determined that a hazard assessment for MB46513 was needed. The HIARC concluded that there were differences as well as similarities between the toxicity profiles for fipronil and MB46513. Differences included the occurrence of thyroid effects, including neoplasia, in the rats treated with fipronil but not MB46513. The mouse does not have any neurologic signs of toxicity at any duration following fipronil exposure, but does following subchronic exposure to MB46513. Although, in the rat, both fipronil and MB46513 result in clinical signs of neurotoxicity, these signs do not appear with fipronil until later (after 90 days). Chronic exposure to the rat with both compounds results in qualitatively and quantitatively similar neurologic effects. Other measured signs of neurotoxicity (observed in the acute neurotoxicity study), appear to occur at about the same dose for both compounds. Therefore, it appears that, in the rat, the differences between the two compounds are qualitative for thyroid effects; but for neurotoxicity, the differences appear to be more quantitative, with longer exposure to fipronil needed in the rat to result in the same clinical signs as MB46513. In the dog, the two compounds are similar for neurotoxicity. In the mouse, there is no neurotoxicity with fipronil, but there is with MB46513. The HIARC concluded that using the acute and chronic reference doses (RfDs) for fipronil to evaluate the risk due to acute and chronic dietary exposure to MB46513 is health protective because the acute and chronic RfDs for MB46513 are based on the same study type with the same neurotoxicity endpoints; thus, the RfDs are similar. The HIARC also determined that the potential for increased susceptibility of infants and children from exposure to MB46513 would be the same as fipronil; therefore, no separate FQPA evaluation is required.

Dose Response Assessment

The acute dietary endpoint is based on decreased hindleg splay (a neurological deficit). The short- and intermediate-term incidental oral endpoints are based on decreased body weight, food consumption, and feed efficiency. Chronic dietary and long-term endpoints are based on increased incidence of seizures and death, alterations in clinical chemistry (protein) and changes in thyroid hormone levels.

This chemical has been classified by the HED Cancer Peer Review Committee (CPRC) as a Group C - Possible Human Carcinogen based on increases in thyroid follicular cell tumors in both sexes of the rat.

Occupational Handler Exposure Assessment

Existing Uses

Fipronil is currently registered for use on cats and dogs for flea control (various formulations) and on turf to control fire-ants (various formulations). Tolerances are established on many raw

agricultural commodities. Registered residential uses of fipronil have been assessed previously by HED and are referenced below.

Proposed Uses

Based upon the proposed use patterns, HED expects the most highly-exposed occupational pesticide handlers are likely to be:

1) seed treatment workers (loader/applicators, sewers, baggers)
2) planters planting treated seed
3) handlers mixing/loading for groundboom application
4) applicator using open-cab ground-boom spray equipment for in-furrow treatment

For some of the application methods, the same individual might perform multiple activities. The HED Science Advisory Council for Exposure (ExpoSAC) draft Standard Operating Procedure (SOP) (29 March 2000) directs that although the same individual may perform all tasks, in some cases they shall be assessed separately.

Margin of Exposure (MOE)

An MOE of 100 is adequate to protect occupational pesticide handlers.

All occupational risk estimates are below HED's level of concern (MOE>100) *provided workers wear protective gloves* when handling fipronil, except for the estimates of risk to seed treatment workers (MOEs of 69 and 18 for dermal and inhalation risk, respectively).

The seed treatment results can be considered conservative due to the exaggerated amount of seed treated, and since they are for workers performing all seed treatment tasks (applying, bagging and sewing). Further clarification on this issue may be forthcoming from IR-4.

Occupational Post-Application

In-Furrow Uses (Potatoes, Sweet Potatoes)

Dermal post-application occupational exposure based on the in-furrow uses of fipronil are expected to be negligible as the soil is normally not contacted after incorporation.

Onion/Shallot Seed Treatment Use

The post-application use scenario for seed treatment uses consists of the grower purchasing bags of treated seed, placing the seed in the hopper and planting the seed in the field. Estimated risks resulted in MOEs of 180 and 130 for dermal and inhalation risk, respectively. Planting of treated seed is not a standardized practice, but HED believes that the estimates presented herein are conservative and may even be an over-estimate of exposure and risk.

Residue Chemistry

Residue chemistry data pertaining to the proposed use of fipronil on potato and onion seed were submitted and reviewed by HED (DP Barcodes: D313293 & 318283, M. Sahafeyan, 8/5/2005). HED recommends a 0.030 ppm tolerance on vegetable, tuberous and corm, subgroup 1C and a 0.03 ppm tolerance on onion, dry bulb.

Residential Exposure Assessments

Residential application and re-entry exposures from the uses of fipronil on pets and from proposed residential uses of fipronil to control fire ants and other outdoor nuisance pests, were assessed previously (DP Barcode: D244048, M. Dow and D. Vogel, 10/24/2000). For dermal and inhalation short- and intermediate-term exposures, all MOEs were greater than 1,500 and for oral short- and intermediate-term exposures, all MOEs were greater than 890. As with the agricultural use of fipronil on cotton, exposure to the photodegradate MB46513 is not expected as a result of residential uses.

Dietary Risk Estimates

Acute and chronic dietary exposure analyses for fipronil were performed using the Dietary Exposure Evaluation Model (DEEM™ version 2.03). Although the acute analyses did not exceed HED's level of concern the **chronic dietary risk did exceed HED's level of concern** (DP Barcode: D324295, B. Hanson, 12/20/2005).

Drinking Water

EFED provided an environmental fate and drinking water assessments for fipronil (+ its 2 metabolites and 1 photodegredate). Drinking water EEC in drinking water on highly vulnerable sites is not likely to exceed **0.006909 ppb** in acute scenarios and **0.003063 ppb** in chronic scenarios.

Aggregate Exposure and Risk Assessment

Aggregate exposure risk assessments were performed for the following: acute aggregate exposure (food + water), short- and intermediate-term aggregate exposure (food + water + residential exposure), and chronic aggregate exposure (food + water). A cancer aggregate risk assessment was *not* performed because HIARC determined that cancer dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the chronic exposure assessment.

Acute aggregate risk estimates are below HED's level of concern. The acute aggregate risk assessment takes into account exposure estimates from dietary consumption of fipronil (food and drinking water). For acute dietary risk estimates, HED's level of concern is >100% acute Population Adjusted Dose (aPAD). The acute analysis was performed assuming tolerance-level

residues and that 100% of each crop was treated for onions and shallots at 0.03 ppm, potato and sweet potatoes at 0.03 ppm, wheat, grain at 0.005 ppm and water (acute) at 0.006909 ppm. Default processing factors were used for all commodities except for potato, flakes and potato, chips, both of which are dried potato commodities. These are usually given the default processing factor of 6.5. HED determined, via residue data, that the processing factors for these commodities are actually <1. Using a processing factor of 1 allows for a more conservative estimate of the acute dietary exposure and risk. Acute dietary risk estimates were 9.8% of the aPAD at the 95th percentile for the general U.S. population and 25% of the aPAD for the highest exposure group, children 1-2 years old. (HED Hot Sheet #12 states that the results of a Tier 2 acute analysis is to be reported at the 95th percentile). The results of the acute analysis indicate that the Tier 2 **acute dietary risk estimates associated with the registered and HED recommended uses of fipronil do not exceed HED's level of concern**. Additional refinement by incorporating %CT information may result in even lower exposure estimates.

Short + Intermediate aggregate risk estimates are below HED's level of concern. HED concludes that short- and intermediate-term aggregate risk for children and adults, respectively, are below HED's level of concern. The Aggregate Risk Index method was used to determine both short- and intermediate-term aggregate risk based on the common endpoint of body weight loss. The short-term risk assessment was conducted, using infants with combined food + water, dermal and oral exposures. The intermediate-term risk assessment was conducted, using Adults 50+ with combined dermal and inhalation exposures. Short- and intermediate term aggregate risk estimates, 1.2 and 2.3, respectively, do not exceed HED's level of concern (i.e. ARIs are greater than or equal to 1).

Chronic aggregate risk estimates exceeded HED's level of concern. For chronic dietary risk estimates, HED's level of concern is >100% of the chronic population adjusted dose (cPAD). For the chronic Tier 1 analysis (assuming tolerance level residues, DEEM™ default processing factors, and 100% CT information), dietary risk estimates exceeded HED's level of concern (>100% cPAD); therefore, a partially refined chronic dietary assessment was performed with use of ARs from field trial data, processing factors where applicable, %CT information and water (chronic) at 0.003063 ppm. Chronic dietary risk estimates were 47% of the cPAD for the general U.S. population and 120% of the cPAD for the highest exposed population subgroup, all infants (< 1 year old); therefore, **chronic dietary risk estimates associated with the registered and HED-recommended uses exceed HED's level of concern**.

A cancer aggregate risk assessment was not performed because HIARC determined that cancer dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the chronic exposure assessment.

Recommendation for Tolerances and Registration

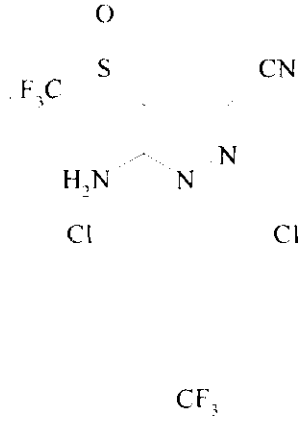
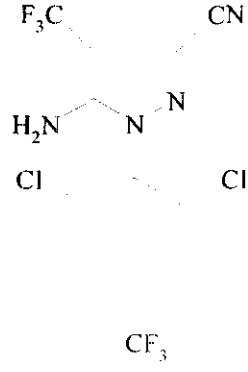
The **agency recommends against the proposed tolerances for fipronil** + metabolites MB46136 and MB45950 + photodegradate MB46513 in/on onion, potatoes, sweet potatoes or corm, subgroup 1C vegetables based on chronic aggregate risk exceeding our level of concern.

2.0. PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1. Identification of Active Ingredient

Chemical Name:	(5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(1R,S)-(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile)
Common Name:	Fipronil
Trade Name:	Regent®
Chemical Type:	Insecticide
PC Code Number:	129121
CAS Registry No.:	120068-37-3
Empirical Formula:	$C_{12}H_4Cl_2F_6N_4$
Molecular Weight:	437.15

2.2. Structural Formula of Fipronil, Metabolites, and Photodegradate

Fipronil	**MB 46513**
	
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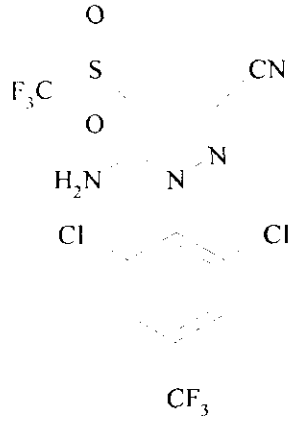
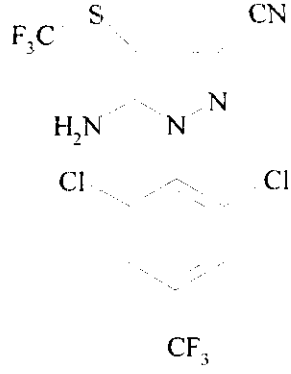
MB 46136	MB 45950
	
5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile	5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)thio]-1H-pyrazole-3-carbonitrile

2.3. Physical and Chemical Properties

Vapor Pressure: 2.8×10^{-9} mm Hg at 20°C
Water Solubility: deionized water: 1.9 mg/L; water, pH 5: 0.0024 g/L; water, pH 9: 0.0022 g/L
Octanol/Water Partition Coefficient: log P_{ow} = 4.01

3.0. HAZARD CHARACTERIZATION

The toxicology database for fipronil is adequate according to the Subdivision F Guideline requirements for a food-use chemical. However, a 28-day inhalation toxicity study in the rat has been requested to further characterize the inhalation risk for use in the risk assessment of fipronil. Acceptable developmental studies in the rat and rabbit, a 2-generation rat reproduction study, and a developmental neurotoxicity rat study are available. There is high confidence in the quality of the existing studies and the reliability of the toxicity endpoints identified for use in risk assessment.

3.1. Hazard Profile

The acute toxicity of fipronil technical is shown in Table1.

Table 1. Acute Toxicity Data on Fipronil Technical.

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity - rat	42918628	LD_{50} = male 92/female 103 mg/kg; male + female 97 mg/kg	II
870.1200 Acute dermal toxicity - rat	42918629	LD_{50} = >2000 mg/kg	III
870.1200 Acute dermal toxicity - rabbit	42918630	LD_{50} = 354 mg/kg	II
870.1300 Acute inhalation toxicity - rat	43544401	LC_{50} = male 0.36/female 0.42 mg/L; male + female 0.39 mg/L	II
870.2400 Acute eye irritation - rabbit	42918632	mild transient ocular irritant	III
870.2500 Acute dermal irritation - rabbit	42918633	slight dermal irritant	IV
870.2600 Skin sensitization - Guinea pig	42918634	non sensitizing	

In acute toxicity studies, fipronil exhibits low to moderate toxicity, depending on the route of exposure and species. Fipronil has moderate acute toxicity (toxicity category II) by the oral and inhalation routes in rats. By the dermal route, it is of moderate toxicity in rabbits, and low toxicity in rats (III). Fipronil technical is relatively non-irritating to the skin (IV) and eye (III) of rabbits and is not a dermal sensitizer. Dermal absorption in rats is estimated to be 1 % or less based on a dermal absorption study.

Fipronil is neurotoxic in both rats and dogs as evidenced by signs in the acute and subchronic screening batteries in the rat; developmental neurotoxicity and chronic carcinogenicity studies in the rat; and in two chronic dog studies. Clinical signs of neurotoxicity were not observed in the mouse or rat at 28 or 90 days. The rat and mouse showed evidence of liver and/or thyroid alterations at all time periods (chronic only for the mouse).

Although there is no evidence of potential for enhanced pre- or post-natal susceptibility in infants and children in the developmental and reproduction studies, the developmental neurotoxicity study identified a developmental NOAEL which was less than the maternal NOAEL indicating an apparent susceptibility issue. However, HIARC concluded that the apparent increased susceptibility in the developmental neurotoxicity study was not supported by the overall weight-of-the-evidence.

Fipronil has been classified by the HED CPRC (document dated 18-Jul-1997) as a Group C - Possible Human Carcinogen, based on increases in thyroid follicular cell tumors in both sexes of the rat, which were statistically significant by both pair-wise and trend analyses. There is no apparent concern for mutagenicity (no mutagenic activity). The RfD methodology should be used to estimate human risk because the thyroid tumors appear to be related to a disruption in the thyroid-pituitary status. Dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the DEEM™ chronic exposure analysis using the RfD.

Fipronil appears to be orally absorbed at a similar rate and extent at low or high dosages. Distribution data showed significant amounts of residual radioactivity in carcass, G.I. tract, liver, adrenals, and abdominal fat at 168 hours post-dose. Repeated low oral dosing or a single high oral dose resulted in an overall decrease in the amount of residual radioactivity found, but an increase in the amount in abdominal fat, carcass, and adrenals. Feces appeared to be the major route of excretion for fipronil derived radioactivity, where 45-75% of an administered dose was excreted. Excretion in urine was between 5-25%. Increases in the percentages excreted in urine and feces were observed with repeated low oral dosing or a single high dose, while the percentage found in all tissues combined decreased. There were no significant sex-related differences in excretion. Major metabolites in urine included two ring-opened products of the metabolite M&B 45,897, two oxidation products (M&B 46,136 and RPA200766), and parent chemical (M&B 46,030). In feces, parent M&B 46,030 was detected as a significant fraction of the sample radioactivity as well as the oxidation products M&B 46,136 and M&B 45,950. Whole blood half-life decreased with increased dosage. The toxicity profile of fipronil (technical) is listed in Table 2.

Table 2. Toxicity Profile of Fipronil Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
	FIPRONIL	
Fipronil 870.3100 28-Day oral toxicity range finding - rat	44028301 (1996) Acceptable/guideline 0, 25, 50, 100, 200, 400 ppm ♂ 0, 3.4, 6.9, 13, 24, 45 mg/kg/day ♀ 0, 3.5, 6.7, 13, 25, 55 mg/kg/day	NOAEL = male <3.4 mg/kg/day LOAEL = 3.4 mg/kg/day based on: (male/female) thyroid follicular hypertrophy, change in protein, and (female) increased liver weight.
Fipronil 870.3100 90-Day oral toxicity - rat	42918643, 43501701 (1991) minimum 0, 1, 5, 30, 300 ppm M 0, 0.70, 0.33, 1.9, 20 mg/kg/day F 0, 0.070, 0.37, 2.3, 24 mg/kg/day	NOAEL = 0.33 mg/kg/day LOAEL = 1.9 mg/kg/day based on: altered serum protein, increased liver, and thyroid weight.

Table 2. Toxicity Profile of Fipronil Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Fipronil 870.3100 90-Day oral toxicity - mouse	44262804 (1991) Acceptable/nonguideline 0, 1, 3, 10, 25 ppm M 0, 0.13, 0.38, 1.3, 3.2 mg/kg/day F 0, 0.17, 0.57, 1.7, 4.5 mg/kg/day	NOAEL = 1.3 mg/kg/day LOAEL = 3.2 mg/kg/day based on: increased body weight gain (BWG).
Fipronil 870.3150 90-Day oral toxicity - dog	42918642 (1991) guideline capsule 0, 0.5, 2.0, 10 mg/kg/day	NOAEL = male 2.0 mg/kg/day, female 0.5 mg/kg/day LOAEL = male 10 mg/kg/day, female 2.0 mg/kg/day based on: clinical signs of toxicity (male/female), and increased BWG (female).
Fipronil 870.3200 21-Day dermal toxicity - rabbit	42918644 (1993) guideline 0, 0.5, 1.0, 5.0, 10 mg/kg/day	systemic NOAEL = 5.0 mg/kg/day LOAEL = 10 mg/kg/day based on: decreased BWG, decreased food consumption (FC), and hyperactivity. dermal NOAEL = 10 mg/kg/day LOAEL = >10 mg/kg/day.
Fipronil 870.3700a Prenatal developmental - rat	42977903 (1991) minimum 0, 1.0, 4.0, 20 mg/kg/day	**Maternal** NOAEL = 4.0 mg/kg/day LOAEL = 20 mg/kg/day based on: decreased BWG, increased water consumption (WC), decreased FC, and decreased food efficiency (FE). **Developmental** NOAEL = 20 mg/kg/day LOAEL =>20 mg/kg/day.
Fipronil 870.3700b Prenatal developmental - rabbit	42918646 (1990) minimum 0, 0.10, 0.20, 0.50, 1.0 mg/kg/day	**Maternal** NOAEL = <0.10 mg/kg/day LOAEL = 0.10 mg/kg/day based on: decreased BWG, decreased FC, and decreased FE. **Developmental** NOAEL = 1.0 mg/kg/day LOAEL = >1.0 mg/kg/day.
Fipronil 870.3800 Reproduction and fertility effects - rat	42918647 (1992) minimum 0, 3.0, 30, 300 ppm M 0, 0.25, 2.5, 26 mg/kg/day F 0, 0.27, 2.7, 28 mg/kg/day	**Parental/Systemic** NOAEL = 0.25 mg/kg/day LOAEL = 2.5 mg/kg/day based on: (male/female) increased thyroid, and liver weight, (female) decreased pituitary weight, and increased follicular epithelial hypertrophy. **Reproductive** NOAEL = 2.5 mg/kg/day LOAEL = 26 mg/kg/day based on: clinical signs, decreased litter size, decreased BW, decreased mating, decreased fertility index, decreased post-implant survival and offspring postnatal survival, and delayed physical development. **Offspring** NOAEL = 26 mg/kg/day LOAEL = >26 mg/kg/day

Table 2. Toxicity Profile of Fipronil Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Fipronil 870.4100a Chronic toxicity - rodent	42918648 (1993) Acceptable/guideline 0, 0.5, 1.5, 300 ppm M 0, 0.019, 0.059, 1.3, 13 mg/kg/d F 0, 0.025, 0.078, 1.6, 17 mg/kg/d	NOAEL = 0.019 mg/kg/day LOAEL = 0.059 mg/kg/day based on: clinical signs, alterations in clinical chemistry, and thyroid parameters.
Fipronil 870.4100b Chronic toxicity - dog	42918645 (1993) Acceptable dietary 0, 0.075, 0.30, 1.0, 3.0/2.0 mg/kg/day (constant conc.)	NOAEL = M 1.0 mg/kg/day; F 0.30mg/kg/day LOAEL = M 2.1 mg/kg/day; F 1.0 mg/kg/day based on: clinical signs of neurotoxicity.
Fipronil 870.4100b Chronic toxicity - dog	42918645 (1992) guideline capsule 0, 0.2, 2.0, 5.0 mg/kg/day	NOAEL = 0.2 mg/kg/day LOAEL = 2.0 mg/kg/day based on: (male/female) decreased BWG, increased liver weight, liver histopath, and (male) decreased FE and clinical signs of neurotoxicity.
Fipronil 870.4200 Carcinogenicity - rat	42918648 (1993) Acceptable/guideline 0, 0.5, 1.5, 300 ppm M 0, 0.019, 0.059, 1.3, 13 mg/kg/d F 0, 0.025, 0.078, 1.6, 17 mg/kg/d	NOAEL = M 0.019 mg/kg/day, F 0.025 mg/kg/day LOAEL = M 0.059 mg/kg/day based on clinical signs, alterations in clinical chemistry, and thyroid parameters. F 0.078 mg/kg/day based on clinical signs, alterations in clinical chemistry, and thyroid parameters. **Evidence of thyroid carcinogenicity.**
Fipronil 870.4300 Carcinogenicity mouse	42918649, 43501702 (1993) minimum 0, 0.10, 0.50, 10, 30, 60 ppm M 0, 0.011, 0.055, 1.2, 3.4 mg/kg/day F 0, 0.012, 0.063, 1.2, 3.6 mg/kg/day	NOAEL = 0.055 mg/kg/day LOAEL = 1.2 mg/kg/day based on decreased BWG, decreased FE, increased liver weight, and liver histopath. **No evidence of carcinogenicity.**
Gene Mutation Fipronil 870.5100 *Salmonella typhimurium* and *Escherichia coli*	42918652 (1988) Acceptable	In two independent experiments, **fipronil** (90.6% a.i.) was not mutagenic in 4 strains of S. typhimurium at concentrations up to 500 µg/plate in the presence or absence of S9 activation.

Table 2. Toxicity Profile of Fipronil Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Gene Mutation Fipronil 870.5300 *In vitro* assay in mammalian cells/Chinese hamster V79 cells	42918651 (1993) Acceptable	In two independent experiments, fipronil (97.2% a.i.) was negative for inducing forward gene mutations at the HGPRT locus in cultured Chinese hamster V79 cells at concentrations up to 385.65 µg/ml both with and without S9 activation.
Cytogenetics Fipronil 870.5375 *in vitro*/human lymphocytes	42918653 (1988) Acceptable	There was no evidence of a clastogenic effect when human lymphocytes were exposed *in vitro* to **fipronil** (90.6% a.i.) at doses of 75, 150 or 300 µg/ml with and without S9 activation.
Cytogenetics Fipronil 870.5395 *In vivo* mouse micronucleus assay	43680801 (1995) Acceptable	There was no evidence of a clastogenic or aneugenic effect at any MB46030 dose or at any harvest time.
Other Effects Fipronil	none	no study
Fipronil 870.6200a - rat Acute neurotoxicity screening battery	42918635 (1993) minimum 0, 0.5, 5.0, 50 mg/kg	NOAEL = 0.5 mg/kg LOAEL = 5.0 mg/kg based on: decreased hindleg splay.
Fipronil 870.6200a - rat Acute neurotoxicity screening battery	44431801 (1997) Acceptable(guideline)	NOAEL = 2.5 mg/kg LOAEL = 7.5 mg/kg based on: (male) decreased hindlimb splay; (female) decreased BW, FC, FE, and grooming.
Fipronil 870.6200b - rat Subchronic neurotoxicity screening battery	43291703 (1993) Acceptable 0, 0.5, 5.0, 150 ppm M 0, 0.030, 0.30, 8.9 mg/kg/day F 0, 0.035, 0.35, 11 mg/kg/day	NOAEL = 0.30 mg/kg/day LOAEL = 8.9 mg/kg/day based on: FOB findings.

Table 2. Toxicity Profile of Fipronil Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Fipronil 870.6300 Developmental neurotoxicity - rat	44039002, 44501102, 44501103 (1995) Acceptable/guideline 0, 0.5, 10, 200 ppm 0, 0.05, 0.90, 15 mg/kg/day	**Maternal** NOAEL = 0.9 mg/kg/day LOAEL = 15 mg/kg/day based on: decreased BW, decreased BWG, and decreased FC. **Developmental** NOAEL = 0.05 mg/kg/day LOAEL = 0.9 mg/kg/day based on decreased pup wt, increased preputial separation time. **Neurotox** NOAEL = 0.9 mg/kg/day LOAEL = 15 mg/kg/day based on decreased auditory startle response, decreased swimming direction scores, group mean angle measurements and water "Y" maze times trails, and decreased absolute brain weight.
Fipronil 870.7485 Metabolism and pharmacokinetic - rat	42918655, 43253701 (1992) minimum 4, 150 mg/kg-single dose 4 mg/kg x 14 days-repeated dose	The rate and extent of absorption appeared similar among all dose groups (4 and 150 mg/kg (single dose) and 4 mg/kg x 14 days (repeated dose)), but may have been decreased at the high dose. Distribution data showed significant amounts of residual radioactivity in carcass, G.I. tract, liver, adrenals, and abdominal fat at 168 hours post-dose for all rats in all dose groups. Repeated low oral dosing or a single high oral dose resulted in an overall decrease in the amount of residual radioactivity found, but an increase in the amount in abdominal fat, carcass, and adrenals. Feces appeared to be the major route of excretion for **fipronil** derived radioactivity (45-75%). Excretion in urine was between 5-25%. Increases in the % excreted in urine and feces were observed with repeated low or a single high doses, while the % found in all tissues combined decreased. There were no significant sex-related differences in excretion. Major metabolites in urine included two ring-opened products of the metabolite M&B 45,897, two oxidation products, and the parent chemical. In feces, parent was detected as a significant fraction of the sample radioactivity as well as the oxidation products. Whole blood half- life ranged from 149-200 hours in male and female rats at 4 mg/kg, with 0-168 hours. Area under curves (AUCs) approximately equal between sexes. At 150 mg/kg, whole blood half life was noticeably decreased to 54.4 hours in male rats and 51.2 hours in female rats. Blood AUCs at this dose were approximately proportional to the increase in dose.
Fipronil 870.7600 Dermal penetration - rat	43737308 (1995) Acceptable	<1% at 24 hours.

3.2. FQPA Considerations

The HIARC concluded that there is no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to fipronil. In the prenatal developmental toxicity studies in rats and rabbits and in the two-generation reproduction study in rats, developmental toxicity occurred at the same doses that caused maternal toxicity. However, the developmental neurotoxicity study identified a developmental NOAEL (0.05 mg/kg/day) which is less than the maternal NOAEL of 0.9 mg/kg/day, indicating an apparent susceptibility issue.

The HIARC, however, determined that the evidence regarding appearance of susceptibility was not convincing due to the equivocal nature of the findings (decrease in offspring body weight and delayed time to preputial separation) at 0.9 mg/kg/day. The HIARC, using a conservative approach, established the LOAEL for offspring developmental toxicity at 0.9 mg/kg/day with the understanding that these effects, although statistically significant, were marginal and appeared to define a threshold response level. This conservative approach resulted in the NOAEL for offspring developmental toxicity (0.05 mg/kg/day) being lower than the NOAEL for maternal toxicity (0.9 mg/kg/day) giving an appearance of increased susceptibility. The HIARC, however, concluded that this increased susceptibility is not valid because the findings in the developmental neurotoxicity study were not supported by the overall weight-of-the-evidence from the fipronil database. Evaluation of the database indicated that: 1) the offspring body weight findings in the developmental neurotoxicity study are not supported by the results of the two-generation reproduction study in rats at similar treatment levels; 2) increased susceptibility to the offspring was not demonstrated following pre- and/or postnatal dosing in the prenatal developmental toxicity study nor the two-generation reproduction study in rats; and 3) no increased susceptibility was seen in the prenatal developmental toxicity study in rats following *in utero* exposure to the photodegradate, MB46513.

The FQPA SFC met on 4/27/98 and recommended that the 10x factor for enhanced sensitivity to infants and children (as required by FQPA) should be **reduced to 1x** for fipronil (Memo, HED Doc. No. 012619, B. Tarplee, 5/12/98). The rationale behind this decision was:

- The HIARC determined that the data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to fipronil. In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

- No increased susceptibility was seen in the prenatal developmental toxicity study in rats following *in utero* exposure to the photodegradate, MB46513.

- The HIARC concluded that the apparent increased susceptibility in the developmental neurotoxicity study was not supported by the overall weight-of-the-evidence.

- Exposure assessments do not indicate a concern for potential risk to infants and children based on: 1) the dietary exposure estimates using field study data and anticipated market share information result in an overestimate of dietary exposure; 2) modeling data is used for ground and surface source drinking water exposure assessments resulting in estimates considered to be reasonable upper-bound concentrations; 3) there is the potential for residential exposure associated with the pet uses, however, the use of chemical and site specific data in the exposure assessment provide a realistic estimate of the potential exposure to infants and children.

3.2.1. Cumulative Risk

EPA does not have, at this time, available data to determine whether fipronil has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that fipronil has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether fipronil shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for fipronil need to be modified or revoked.

3.2.2. Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, fipronil may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

3.3. Dose Response Assessment

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 3.

Table 3. Summary of Toxicological Dose and Endpoints for Fipronil for Use in Human Risk Assessment [1].

Exposure Scenario (Fipronil)	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary all populations including infants and children	NOAEL= 2.5 mg/kg UF = 100 **Acute RfD** = 0.025 mg/kg	FQPA SF = 1 **aPAD** = acute RfD / FQPA SF = 0.025 mg/kg	Acute neurotoxicity - rat LOAEL = 7.0 mg/kg based on: decreased hindleg splay in males at 7 hours.
Chronic Dietary all populations	NOAEL= 0.019 mg/kg/day UF = 100 **Chronic RfD** = 0.0002 mg/kg/day	FQPA SF = 1 **cPAD** = chr RfD / FQPA SF = 0.0002 mg/kg/d	Chronic/carcinogenicity study - rat LOAEL = 0.059 mg/kg/day based on: increased incidence of seizures and death, alterations in clinical chemistry (protein), increased TSH, and decreased T4.
Short-Term Oral (1-7 days) (Residential)	oral study LOAEL ≤0.1 mg/kg/day UF of 3 for no NOAEL, 100 for interspecies extrapolation and intraspecies variation	**LOC for MOE** = 300 (Residential, includes the FQPA SF)	Developmental toxicity Study - rabbit LOAEL = ≤ 0.1 mg/kg/day based on: maternal toxicity of decreased body weight gain, decreased food consumption, and decreased food efficiency.
Intermediate-Term Oral (1 week - several months) (Residential)	oral study LOAEL ≤0.1 mg/kg/day UF of 3 for no NOAEL, 100 for interspecies extrapolation and intraspecies variation	**LOC for MOE** = 300 (Residential, includes the FQPA SF)	Developmental Toxicity Study - rabbit LOAEL = ≤ 0.1 mg/kg/day based on: maternal toxicity of decreased body weight gain, decreased food consumption, and decreased food efficiency.
Short-Term Dermal (1-7 days) (Occupational/ Residential)	dermal study NOAEL= 5 mg/kg/day	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes FQPA SF)	21-Day dermal toxicity study - rabbit LOAEL = 10.0 mg/kg/day based on: decreased body weight gain, and food consumption in both sexes.

Table 3. Summary of Toxicological Dose and Endpoints for Fipronil for Use in Human Risk Assessment [1].

Exposure Scenario (Fipronil)	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Intermediate-Term Dermal (1 week - several months) (Occupational/ Residential)	dermal study NOAEL= 5 mg/kg/day	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes FQPA SF)	21-Day dermal toxicity study - rabbit LOAEL = 10.0 mg/kg/day based on: decreased body weight gain, and food consumption in both sexes.
Long-Term Dermal (several months - lifetime) (Occupational/ Residential)	oral study NOAEL= 0.019 mg/kg/day (dermal absorption rate = 1%)	**acceptable MOE** = 100 (Occupational) **acceptable MOE** = 100 (Residential, includes FQPA SF)	Chronic/carcinogenicity study - rat LOAEL = 0.059 mg/kg/day based on: increased incidence of seizures and death, alterations in clinical chemistry (protein), increased TSH, and decreased T4.
Short-Term Inhalation (1-7 days) (Occupational/ Residential)	oral study NOAEL= 0.05 mg/kg/day (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes FQPA SF)	Developmental neurotoxicity - rat LOAEL = 0.90 mg/kg/day based on: decrease in group mean pup weights during lactation, and significant increase in time of preputial separation in males (dietary).
Intermediate-Term Inhalation (1 week - several months) (Occupational/ Residential)	oral study NOAEL= 0.05 mg/kg/day (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes FQPA SF)	Developmental neurotoxicity - rat LOAEL = 0.90 mg/kg/day based on: decrease in group mean pup weights during lactation, and significant increase in time of preputial separation in males (dietary).
Long-Term Inhalation (several months - lifetime) (Occupational/ Residential)	oral study NOAEL= 0.019 mg/kg/day (inhalation absorption rate = 100%)	**acceptable MOE** = 100 (Occupational) **acceptable MOE** = 100 (Residential, includes FQPA SF)	Chronic/carcinogenicity rat study LOAEL = 0.059 mg/kg/day based on: increased incidence of seizures and death, alterations in clinical chemistry (protein), increased TSH, and decreased T4.
Cancer (oral, dermal, inhalation)	Group C - possible human carcinogen	Use chronic RfD to estimate human risk	Increases in thyroid follicular cell tumors with fipronil (male/female)

[1] UF = uncertainty factor, FQPA SF = FQPA Safety Factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, LOC = level of concern, MOE = margin of exposure.

Acute Dietary Endpoint: The rat acute oral neurotoxicity study was used to select the endpoint for the acute RfD of 0.025 mg/kg for the general U.S. population (including infants and

children). The NOAEL of 2.5 mg/kg was based on decreased hindleg splay in males at 7 hours post-dosing at the LOAEL of 7.0 mg/kg. These effects occurred following a single dose in the acute neurotoxicity study and therefore are appropriate for use in the acute dietary risk assessment. An UF of 100 was established for intraspecies variation (10x) and interspecies extrapolation (10x). The FQPA SFC determined that the SF of 1x is applicable for this acute dietary risk assessment. Thus, the aPAD for the general U.S. population (including infants and children) is equivalent to the acute RfD of 0.025 mg/kg.

Chronic Dietary Endpoint: The rat combined chronic toxicity/carcinogenicity study was used to select the endpoint for establishing the chronic RfD of 0.0002 mg/kg/day. The NOAEL of 0.019 mg/kg/day was based on increased incidences of seizures and death, alterations in clinical chemistry (protein), and increased TSH and decreased T4 blood levels at the LOAEL of 0.059 mg/kg/day. An UF of 100 was established for intraspecies variation (10x) and interspecies extrapolation (10x). The FQPA SFC determined that the SF of 1x is applicable for chronic dietary risk assessment. Thus, the cPAD is equivalent to the chronic RfD of 0.0002 mg/kg/day.

Carcinogenicity: This chemical has been classified by the HED CPRC (document dated July 18, 1997) as a Group C - Possible Human Carcinogen. The RfD methodology should be used to estimate human risk because the thyroid tumors appear to be related to a disruption in the thyroid-pituitary status.

Short- and Intermediate-Term Incidental Oral: Short- and intermediate-term oral incidental endpoints were selected from a rabbit developmental study. The LOAEL of 0.1 mg/kg/day was based on maternally toxic effects including decreased body weight gains, food consumption, and food efficiency. No NOAEL was established in this study.

Dermal Penetration: The dermal absorption factor is 1%.

Short- and Intermediate-Term Dermal Endpoint: A short- and intermediate-term dermal endpoint was selected from a rabbit 21-day dermal toxicity study. The NOAEL of 5 mg/kg/day was based on decreased body weight gain and food consumption in both sexes at the LOAEL of 10 mg/kg/day. This dose/endpoint is appropriate for short- and intermediate-term exposure risk assessment.

Long-term Dermal Endpoint: A long-term dermal endpoint was selected from a rat combined chronic toxicity/carcinogenicity study. The NOAEL of 0.019 mg/kg/day was based on an increased incidence of seizures and death, alterations in clinical chemistry (protein), and increased TSH and decreased T4 blood levels at the LOAEL of 0.059 mg/kg/day. This dose/endpoint is appropriate for long-term exposure risk assessment. Since an oral NOAEL was used for dermal risk assessment, the dermal absorption factor of 1% was used.

Short- and Intermediate-term Inhalation Endpoint: A short- and intermediate-term inhalation endpoint was chosen from a rat developmental neurotoxicity study. The NOAEL of 0.05 mg/kg/day was based on decreased group mean pup weights during lactation and increased preputial separation in males at the LOAEL of 0.90 mg/kg/day. This dose/endpoint is

appropriate for short- and intermediate-term exposure risk assessment. An inhalation absorption factor of 100% was used.

Long-term Inhalation Endpoint: A long-term inhalation endpoint was selected from a rat combined chronic toxicity/carcinogenicity study. The NOAEL of 0.019 mg/kg/day was based on an increased incidence of seizures and death, alterations in clinical chemistry (protein), and increased TSH and decreased T4 blood levels at the LOAEL of 0.059 mg/kg/day. This dose/endpoint is appropriate for long-term exposure risk assessment. An inhalation absorption factor of 100% was used.

MOE for Occupational/Residential Risk Assessments: The level of concern for MOEs for short- and intermediate-term incidental oral risk assessment is 300. The level of concern for MOEs for dermal and inhalation occupational and non-occupational exposure risk assessment is 100. For long-term dermal and short-, intermediate-, and long-term inhalation exposures, the following route-to-route extrapolation was followed: the inhalation (using 100% absorption) and dermal (using 1% absorption) exposures were converted to equivalent oral doses, combined, and then compared to their respective oral NOAELs since one of the dermal and all of the inhalation endpoints are based on oral equivalents.

4.0. EXPOSURE ASSESSMENT

4.1. Summary of Proposed Uses

Table 4. Summary of Directions for Use of Fipronil.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Onion Seed (dry bulb), Garlic Seed (dry bulb), Shallot Seed (dry bulb)						
Seed treatment using any equipment capable of applying viscous liquid products	Regent® TS [7969-223]	0.025 lb ai/ lb of seed	NA	NA	NA	Treated seed must have unnatural appearance or color to indicate that the seed is treated.

Tuberous and corm vegetables subgroup (Crop Subgroup 1-C)						
1 in-furrow applic. at planting by liquid spray system	Regent® 4 SC [7969-207]	0.0975-0.13 lb ai/A	1	0.13 lb ai/A	90	Do Not apply in row spacing less than 30 inches.

Onion Seed (dry bulb), Garlic Seed (dry bulb), Shallot Seed (dry bulb)

The petitioner has submitted one revised label, Regent® 4 TS with directions for use of fipronil on onion seed (dry bulb), garlic seed (dry bulb), and shallot seed (dry bulb). Regent® 4 TS is an aqueous flowable formulation 56% fipronil content. The proposed use allows 0.025 lb ai (0.5 oz) /lb seed for control of onion maggot.

Potato / Sweet Potato (crop subgroup 1-C)

The petitioner has submitted one revised label, Regent® 4 SC with directions for use of fipronil on field corn and potato/sweet potato. Regent® 4 SC is a suspension concentrate with approximately 39% fipronil. The proposed uses allow only one in-furrow application at planting to potato or sweet potato for a maximum of 0.10 lb (3.2 oz) ai/A/season for the control of wire worms (both sweet and white potatoes) and cucumber beetles (only in sweet potatoes). A PHI of 90 days was proposed. The label provides a chart where the rate can be adjusted according to row spacing and row ft. per acre. The PBI restrictions are not stated for potato and sweet potato use. Fipronil is not currently registered in Arizona or California. The available rotational crop data support PBIs of 2 months for wheat and 4 months for leafy and legume vegetables. Rotation to all other crops (except registered crops) should be prohibited. A revised Section B reflecting PBI restrictions on Regent® 4 SC label [EPA Reg. No. 7969-207] should be submitted.

4.2. Dietary Exposure

4.2.1. Food Exposure

Residue chemistry data pertaining to the proposed use of fipronil on potato and onion seed were submitted and reviewed by HED (DP Barcode: D313293 & 318283, M. Sahafeyan, 8/5/2005).

4.2.1.a. Nature of the Residue - Plants and Livestock

Plants

Based on a cursory review of the submitted potato metabolism study (MRID No. 44262832), HED determined that this study is not relevant to this petition. This is because the application of fipronil in the metabolism study was conducted foliar instead of in-furrow; crop is a tuber. Exaggerated rate of foliar applications (5x) was also immaterial based on submitted magnitude of

residue studies on potato (MRID No. 44604802) showing residues in/on potato tubers are predominantly due to in-furrow applications.

The results of the previously submitted confined rotational crop studies are more relevant. In that study [phenyl-^{14}C]-fipronil was applied to outdoor plots at a rate of 0.15 lbs. ai/A (1.5X). Lettuce, carrots and grain sorghum were planted 30 days after treatment (DAT); lettuce, radishes and winter wheat were planted 153 DAT; and lettuce, radishes and grain sorghum were planted 365 DAT. The TRR in the 30-DAT crops ranged from 0.003 ppm (lettuce) to 0.036 ppm (sorghum stover); in 153-DAT crops, from 0.003 ppm (radish root) to 0.172 ppm (wheat straw); and in 365-DAT crops, from 0.003 ppm (radish root) to 0.024 ppm (sorghum stover). No additional metabolites of concern (than what is currently determined to be the residues of concern) were identified from 30-DAT carrots and 153-DAT radishes.

HED's Conclusion: The residues of concern are fipronil and its metabolites MB46136 and MB45950 and photodegradate MB46513 (DP Barcode: D236164, R. Loranger, 6/5/97). BASF should correct the chemical name for MB46136 as: (5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile); thus, a revised section F is also required.

Livestock

The nature of the residue in livestock is understood. Fipronil is metabolized by: 1) hydrolysis to the amide (RPA 200766), 2) oxidation to the sulfone MB46136, or 3) reduction to MB45950. The HED Metabolism Assessment Review Committee (MARC), in a meeting held on 5/28/97, has determined that the fipronil residues of concern for the tolerance expression and dietary risk assessment in livestock commodities are the parent, the metabolites MB46136 and MB45950, and photodegradate MB46513 (DP Barcode: D236164, R. Loranger, 6/5/97). Even though the photodegradate MB46513 is not an animal metabolite, it is included in the tolerance expression for livestock commodities in order to account for the transfer of secondary residues to livestock feed items and then to human consumption.

4.2.1.b. Residue Analytical Method - Plants and Livestock

Plants

An adequate enforcement method (Method EC-95-303, MRID No. 43776604) is available for the determination of fipronil + metabolites MB46136 and MB45950 + photodegradate MB46513 in cotton, corn, potato, and rice RACs as well as their processed fractions. A PMV was successfully completed on cotton with minor revisions recommended by the ACL (DP Barcode: D234562, G. Kramer, 4/29/97). Briefly, samples are extracted by homogenization in acetonitrile/water (75/25). Solids are removed by filtration and NaCl is added to the extract. After clean-up by liquid/liquid partitioning with hexane, the acetonitrile is removed by rotary evaporation. The aqueous solution is then extracted with dichloromethane. The dichloromethane solution is concentrated and cleaned-up using column chromatography.

Fipronil + metabolites MB46136 and MB45950 + photodegradate MB46513 are then analyzed using GC/ECD.

The registrant submitted additional data for Method EC-95-303 (MRID No. 44605506) to address minor revisions to the method recommended by ACL. The appropriate changes were made to the method. The Method EC-95-303 was found acceptable for enforcement by the ACL and have been forwarded to the FDA to be included in PAM II. The requirements for analytical enforcement methodology are fulfilled. The limit of quantitation (LOQ) is 0.005 ppm for cottonseed, meal, hulls, crude and refined oils, and 0.01 ppm for cotton gin byproducts.

In potato study samples were analyzed for fipronil and its metabolites of concern (MB46136, MB45950, MB46513) using GC/ECD. The method LOQ for each compound was 0.003 ppm. The limit of detection (LOD) was not reported. Procedural recovery samples were fortified from 0.003 ppm to 0.030 ppm. A recovery sample fortified at levels to reflect residues found in treated samples was included with each set of treated samples analyzed. The recoveries in fortified samples averaged from the lowest of 79% $\pm$ 4% (for MB45950 fortified at 0.030 ppm) to the highest of 140% $\pm$ 25% (for MB46136 fortified at 0.030 ppm).

In onion study, sample were analyzed for fipronil and its metabolites of concern (MB46136, MB45950, MB46513) using GC/ECD. The validated LOQs for fipronil, MB45950, MB46136, and MB46513 in/on onion-dry bulb is 0.005 ppm. The calculated LODs ranges from 0.00053 ppm to 0.0014 ppm for fipronil, and its metabolites. Concurrent average recoveries of MB46513, MB45950, fipronil, and MB46136 at 0.005 ppm averaged 102−16, 91$\pm$3, 104$\pm$8 (n=11) and 104$\pm$8 (n=10), respectively; ranging from 82% to 130% for all the four compounds.

Livestock

A method for the determination of residues of fipronil and its metabolites MB45950 and MB46136 in livestock commodities was previously reviewed in conjunction with a petition for corn and livestock RACs (DP Barcode: D214376, G. Kramer, 7/25/95 and DP Barcode: D222350, G. Kramer, 4/1/96). It has undergone a successful PMV (DP Barcode: D220222, G. Kramer, 10/26/95) and a revised method has been submitted. The requirements for analytical enforcement methodology are fulfilled (DP Barcode: D222350, G. Kramer, 4/1/96). The livestock method have been forwarded to FDA for inclusion in PAM II.

All previously-cited deficiencies are resolved; details are covered in a previous memorandum (DP Barcode: D236359, S. Levy, 2/15/2005).

4.2.1.c. Multiresidue Methods

Acceptable recoveries of MB46513 were obtained in corn forage using Protocol E and cottonseed using Protocol F. Recoveries were 98.6 $\pm$ 9.4% using Protocol E and 89 $\pm$ 6.2% using Protocol F. All deficiencies are resolved; details are covered in a previous memorandum (DP Barcode: D236359, S. Levy, 2/15/2005).

4.2.1.d. Storage Stability Data

44262833.der
45731401.der

An adequate storage stability study was submitted in support of the petition for Section 3 registration of potato and sweet potato (44262833.der.wpd). Samples of chopped potatoes spiked with fipronil (CAS #: 120068-37-3, 99.3% a.i.), and its metabolites MB46136 (CAS#120068-36-2, 99.9% a.i.), MB45950 (CAS#120067-83-6, 98.8% a.i.), and MB46513 (CAS# not available, 98.5% a.i.) at a level of 0.1 ppm were stored at -20 °C for a duration of 24 months. Under these conditions, residues of fipronil and its metabolites were stable; i.e., the lowest recovery was for MB46513 at 88% ± 9% and the highest was for fipronil at 92% ± 11% recovery in potato tuber samples (Table 5). The method of analysis was "Insecticide, Fipronil: Analytical Method for the Determination of Fipronil and its Metabolites in Cotton and Potatoes," Rhône-Poulenc Ag Company document number 44671, issued on July 21, 1995. The LOQ was 0.005 ppm. The storage stability data indicate that residues of fipronil, MB46136, MB45950, and MB46513 are stable at -20 °C for 24 months in potato tubers.

An adequate storage stability study was submitted in conjunction with the magnitude of residue study on dry-bulb onion seed treatment (45731401.der.wpd). Samples were stored under frozen (-21 ± 7°C) condition for 281 days. The three storage recovery samples for each of MB46513, MB45950, fipronil, and MB46136 on dry-bulb onion controls spiked at 0.010 ppm of all four chemicals averaged to 97%+4, 84%+6, 92%+3 and 95%+5, ranging from 79% to 100% for all the four compounds (Table 6). These data support storage stability of the field samples which were stored for 204 days.

All previously-cited deficiencies are resolved; details are covered in a previous memorandum (DP Barcode: D236359, S. Levy, 2/15/2005).

Table 5. Stability of Residues of Fipronil and Its Metabolites in Potatoes Following Storage at -20°C.

Commodity	Spike level (mg/kg)	Storage interval (months)	Recovered residues (mg/kg)	Corrected % recovery[1]
Fipronil				
potato tuber	0.1	1	0084 0.081	90 87
		3[2]	0.078 0.090	88 101
		6	0.072 0.074	92 94
		9	0.068 0.081	87 103
		12	0.070 0.083	72 85

Table 5. Stability of Residues of Fipronil and Its Metabolites in Potatoes Following Storage at -20°C.

Commodity	Spike level (mg/kg)	Storage interval (months)	Recovered residues (mg/kg)	Corrected % recovery[1]
		24	0.064 0.079	94 116
MB45950				
potato tuber	0.1	1	0.080 0.072	91 82
		3	0.068 0.080	85 99
		6	0.062 0.066	85 90
		9	0.067 0.079	82 97
		12	0.061 0.070	71 82
		24	0.063 0.075	93 110
MB46136				
potato tuber	0.1	1	0.084 0.082	84 82
		3	0.074 0.088	78 94
		6	0.077 0.079	88 90
		9	0.083 0.094	78 89
		12	0.071 0.084	67 80
		24	0.074 0.086	91 106
MB46513				
potato tuber	0.1	1	0.085 0.077	90 82
		3	0.078 0.087	86 96
		6	0.072 0.074	88 90
		9	0.080 0.096	81 97
		12	0.075 0.087	76 89

Table 5. Stability of Residues of Fipronil and Its Metabolites in Potatoes Following Storage at -20°C.				
Commodity	**Spike level (mg/kg)**	**Storage interval (months)**	**Recovered residues (mg/kg)**	**Corrected % recovery[1]**
		24	0.061 0.084	78 106

[1] Corrected for concurrent-recoveries
[2] control sample contained 0.001ppm Fipronil

Table 6. Summary of Storage Stability Study					
Matrix (RAC or Extract)	**Storage Temp. (°C)**	**Storage Interval (day)**	**% recovery (average)**	**% Concurrent Recovery (spiked at 0.010 ppm)**	**Corrected % recovery**
Fipronil (fortified at 0.010 ppm)					
Onion-dry bulb (ground)	-21 ± 7°C	281 days	95, 93, 89	79	120, 118, 113
MB46513 (fortified at 0.010 ppm)					
Onion-dry bulb (ground)	-21 ± 7°C	281 days	100, 98, 92	86	116, 114, 107
MB45950 (fortified at 0.010 ppm)					
Onion-dry bulb (ground)	-21 ± 7°C	281 days	90, 84, 79	72	125, 117, 110
MB46136 (fortified at 0.010 ppm)					
Onion-dry bulb (ground)	-21 ± 7°C	281 days	100, 94, 90	80	125, 118, 113

4.2.1.e. Crop Field Trials

With BASF withdrawal of petition for fipronil use on cotton, all deficiencies cited in previous memorandum (DP Barcode: D219819, G. Kramer, 11/12/1996) regarding cotton registration are disregarded.

Potato

44604802.der (potato)

Rhône-Poulenc Ag Co. has submitted the results of a potato magnitude of residue study with fipronil in 1996 from 17 trials conducted in Regions 11 (n=5), 5 (n=4), 9 (n=2), 10 (n=1), 2 (n=2), 3 (n=1), 1 (n=2). Three treatment regimes were conducted. Each field trial site consisted of one untreated control plot and one treated plot. The first treatment regime was conducted in all 17 sites in which one in-furrow application at ~0.1 lb a.i./A using 200SC formulation (200 g/L suspension concentrate) was followed by four foliar applications, each at 0.05 lb ai/A of

200SC with 7-day RTI and 28-day PHI. The second treatment regime was conducted in 4 sites with the same rates as in the first treatment regime, however, a 1.5% granular formulation was used instead of 200SC formulation for in-furrow application. The aim of the second treatment regime was to investigate the effect of formulation for in-furrow treatment. The third treatment regime was conducted at 2 sites in which only an in-furrow application at planting (no foliar application) was performed at 0.1 lb a.i./A using the 1.5% granular formulation.

Duplicate samples of treated and single samples of untreated crops were collected by hand (~24 tubers per sample) and sent to the analytical laboratories in frozen conditions. Samples were kept frozen from collection to extraction for 342 - 462 days. The submitted storage stability data on potatoes (MRID No. 44604801, under review) indicate that fipronil residues in frozen potatoes are stable for up to 24 months.

Samples were analyzed for fipronil and its metabolites of concern (MB46136, MB45950, MB46513) using GC/ECD. The LOQ for each compound was 0.003 ppm. The LOD was not reported. Procedural recovery samples were fortified from 0.003 ppm to 0.030 ppm. A recovery sample fortified at levels to reflect residues found in treated samples was included with each set of treated samples analyzed. The recoveries in fortified samples averaged from the lowest of 79% ± 4% (for MB45950 fortified at 0.030 ppm) to the highest of 140% ± 25% (for MB46136 fortified at 0.030 ppm).

The total residues of fipronil (i.e., fipronil + metabolites of concern) in treated samples from treatment 1 ranged from 0.012 ppm to 0.028 ppm with the highest average field trial (HAFT) of 0.024 ppm. The total residues of fipronil in treated samples from treatment 2 ranged from 0.010 ppm to 0.019 ppm with the HAFT at 0.024 ppm. The total residues of fipronil in treated samples from treatment 3 ranged from 0.012 ppm to 0.026 ppm with the HAFT at 0.019 ppm. The calculated tolerance based on 95% confidence interval of 95th percentile of the field trial data (with assumption of log-normality) is 0.030 ppm; correction for censored data (<LOQ) using MLE technique yields an 0.025 ppm value. See Table 7 for a summary of potato crop field trial residue data.

HED's Conclusion: Trial numbers and geographical locations are adequate. HED recommends a 0.030 ppm tolerance on vegetable, tuberous and corm, subgroup 1C.

Table 7. Summary of Residue Data from Potato Crop Field Trials with Fipronil.

Commodity	Total Applic. Rate, (lb a.i./A)	PHI (days)	Total Residues (Fipronil + Metabolites MB46136, MB45950 and MB46513) in ppm						
			n	Min.	Max.	HAFT*	Median	Mean	Std. Dev.
Treatment 1 (SC in-furrow + 4 times SC foliar applications)									
potato tubers	0.3	27-35	34	0.012	0.028	0.024	0.012	0.012	0.0048
Treatment 2 (granular in-furrow + 4 times SC foliar applications)									

potato tubers	0.3	28-35	8	0.010	0.019	0.017	0.010	0.009	0.004
Treatment 3 (in-furrow application at planting)									
potato tubers	0.1	NA	4	0.012	0.026	0.019	0.013	0.014	0.006

1 For the calculation of minimum and maximum values, the LOQ value for each analyte (0.003 ppm) was used for residues reported as ND or <LOQ in Table C.3. For calculation of the median, mean, and standard deviation, ½ LOD (0.0005 ppm) was used for residues reported as ND and ½ LOQ (0.0015 ppm) was used for residues reported between the LOQ and LOD.

Onion

45731401.der (onion)

Interregional Research Project No. 4 (IR-4), on behalf of the Agricultural Experiment Stations of Michigan and Texas, has submitted 9 field trial data for fipronil on onion (dry bulb) as a seed treatment application. The trials were conducted in EPA Regions 1 (n=1), 5 (n=2), 6 (n=1), 8 (n=1), 10 (n=2), 11 (n=1), and 12 (n=1). The number and locations of field trials are in accordance with OPPTS Guideline 860.1500. The seeds were treated with EXP81020A (a flowable suspension containing 500 g ai/L, supplied by Aventis Crop Sciences, NC) at a rate of 24.87 g ai/Kg (2.49 lb ai/100 lb) of seed to 25.11 g ai/Kg (2.51 lb ai/100 lb) of seed. The seed (both treated and untreated control) had been also treated with Thiram 42S and a dye (Pro-Ized® Seed Colorant). Each field trial site consisted of one untreated control plot and one treated plot. At each site, duplicate samples of onion (dry bulb), with each sample consisting of 24 or more bulbs, were collected by hand with a PHI of 114-281 days. Samples from all sites except three (NM15, TX04, and WA01) were placed in a freezer within 2 hours and 10 minutes and sent to IR-4 Analytical Laboratories (Cornell University-NYSAES, Geneva, NY 14456-0462). Samples from the three sites mentioned above were collected after the plants were harvested and left in the field to dry as is done commercially. Samples were kept for up to 204 days (from collection to analysis) under -21±7 °C before being analyzed.

The analytical method was developed by Rhône-Poulenc AG Company and modified by IR-4 Laboratories. In this method, samples are homogenized in acetonitrile/acetone, cleaned up by column chromatography and analyzed by GC/ECD. The validated LOQs for fipronil, MB45950, MB46136, and MB46513 in/on onion-dry bulb is 0.005 ppm. The calculated LODs ranges from 0.00053 ppm to 0.0014 ppm for fipronil, and its metabolites. Samples were stored under frozen (-21 ± 7°C) condition for 281 days. The three storage recovery samples for each of MB46513, MB45950, fipronil, and MB46136 on dry-bulb onion controls spiked at 0.010 ppm of all four chemicals averaged to 97%+4, 84%+6, 92%+3 and 95%+5, ranging from 79% to 100% for all the four compound. These data support storage stability of the field samples which were stored for 204 days. Concurrent average recoveries of MB46513, MB45950, fipronil, and MB46136 at 0.005 ppm averaged 102+16, 91±3, 104±8 (n=11) and 104±8 (n=10), respectively; ranging from 82% to 130% for all the four compounds.

MB46513, MB45950 and MB46136 residues on treated dry bulb onion samples were found to be below the LOQ (0.005 ppm) and residues of fipronil across all samples ranges from <LOQ - 0.018 ppm. The combined residues (fipronil and its metabolites MB46513, MB45950 and

MB46136) range from <0.02 - <0.033 ppm. See Table 8 for a summary of dry-bulb onion seed treatment residue data.

HED's Conclusion: Trial numbers and geographical locations are adequate. HED recommends a 0.03 ppm tolerance on onion, dry bulb.

Table 8. Summary of Residue Data from Dry-Bulb Onions Seed Treatment with Fipronil.

Commodity	Total Applic. Rate, (Lb ai/ 100 lb seed)	PHI (days)	Total Residues (Fipronil + Metabolites MB46136, MB45950 and MB46513) in ppm					
			n	Min.	Max.	HAFT*	Mean	Std. Dev.
Fipronil, MB46513, MB45950 and MB46136								
Onion-dry bulb	2.487 - 2.492	114-281	18	<0.020	<0.033	<0.028	<0.021	0.003

4.2.1.f. Processed Food/Feed

44262835.der

All previously-cited deficiencies are resolved; details are covered in a previous memorandum (DP Barcode: D236359, S. Levy, 2/15/2005).

Fipronil, as a 80% a.i. wettable-granule formulation (Regent 800 WG) was applied to potatoes at a total rate of 2.0 lb ai/A (an in-furrow application at planting of 1.0 lb ai/A followed by four foliar applications at 0.25 lb ai/A at 72, 57, 41, and 28 days before harvest). The potato tubers were processed into chips, flakes and wet peels. The analytical method EC-95-303 entitled "Insecticide, Fipronil: Analytical Method for the Determination of Fipronil and its Metabolites in Cotton and Potatoes" was used to quantitate residues of fipronil and its metabolites MB45950, MB46136, and MB46513. Adequate method validation data was provided with previous studies and adequate concurrent recovery data was provided with this study. In this method potato and potato processed fractions are extracted with acetonitrile:acetone (70:30, v/v) and cleaned up by column chromatography. Residues were quantitated by GC/ECD. The LOQ was 0.005 ppm for each analyte. Samples were stored for maximum of 31 days. Since a submitted storage-stability study on potatoes (DP Barcode: D3138283, 44262833.der) indicates that fipronil and its metabolites of concern are stable under frozen conditions for 24 months no storage stability data are required. A comparison of the residues in the raw agricultural commodity (RAC) with those in each processed fraction resulted in concentration factors of 0.40, 0.47, and 6.8 for potato chips, flakes and wet peels respectively. However, since the empirical processing factor for wet peels (6.8) was greater than the maximum theoretical concentration factor (4.0; Table 3 in 860.1520 Residue Chemistry Guidelines), the latter (4.0) was used as the processing factor. HED recommends a 0.10 ppm tolerance on potato wet peel based on HAFT residue level in potato trials (0.024 ppm) and a concentration factor of 4.0; i.e., 4.0 X 0.024 = 0.096 ppm.

4.2.1.g. Meat, Milk, Poultry and Eggs

Secondary residues are expected in livestock commodities associated with registered and proposed uses. Meat/milk/poultry/egg tolerances have been established as a result of other fipronil uses (40 CFR §180.517a: fat of cattle, goat, horse and sheep, 0.40 ppm; liver of cattle, goat, horse and sheep, 0.10 ppm; meat byproducts (except liver) of cattle, goat, horse and sheep, 0.04 ppm; meat of cattle, goat, horse and sheep, 0.04 ppm; hog fat, 0.04 ppm; hog liver, 0.02 ppm; hog meat, 0.01 ppm; hog meat byproducts (except liver), 0.01 ppm; milk, fat (reflecting 0.05 ppm in whole milk), 1.50 ppm; poultry fat, 0.05 ppm; poultry meat, 0.02 ppm; poultry meat byproducts, 0.02 ppm; and eggs, 0.03 ppm). HED estimates indicate that no increases in theoretical dietary burden for livestock are expected from withdrawal of cotton feed items and addition of potato feed items (culls and processed waste). Therefore, HED recommends that existing tolerances on livestock be maintained.

4.2.1.h. Confined Accumulation in Rotational Crops

Deficiency - Conclusion 2a (DP Barcode: D219819, G. Kramer, 11/12/1996)

2a. Based on the results of the confined rotational crop study, the minimum possible PBI for root and leafy vegetables is 5 months and limited and/or extensive rotational field trials are required in order to determine the appropriate intervals for small grains and all other crops (Memo, D228385, G. Kramer, 8/26/96). A statement should be added to the Fipronil 80 WG label which restricts rotational crops to root and leafy vegetables (5-month minimum) and cotton (anytime).

4.2.1.i. Field Accumulation in Rotational Crops

To fulfil the deficiency cited in G. Kramer Memorandum (11/12/1996), Rhône-Poulenc Ag Company conducted a study (MRID No. 45120013, reviewed by S. Levy, DP Barcode: D236359, 2/15/01) in which two limited field trials were conducted in the states of NC and CA in 1995. Regent® 80 WG was applied at a rate of 0.30 lbs. ai/A (1.5X) to bare soil. Rotational crops were planted 30, 120, 240, and 365 days after application. At each interval, 4 crops were selected for planting from the following crop groups: leafy vegetables, legume vegetables and small grains. After harvest at normal maturity, samples were stored frozen until analysis (355-796 days). Samples were analyzed for fipronil, MB46513, MB46136, and MB45950 using a slight modification of the proposed analytical enforcement method for cotton. The LOD was reported to be 0.002 ppm and the LOQ was reported to be 0.005 ppm. The average procedural recovery for fipronil was 71.0 ± 11.6% (n=39); for MB46513, 97.6 ± 6.4% (n=39); for MB46136, 84.2 ± 13.0% (n=39); and for MB45950, 82.9 ± 6.8% (n=39). Analysis of the treated samples showed that residues of MB46513 >0.01 ppm were found in all rotational crops at 30 days after treatment (DAT), in wheat straw at 119 and 239 DAT, and in sorghum straw at 367 DAT. Residues of MB46136 >0.01 ppm were found in lettuce and sorghum straw at 30 DAT, in wheat straw at 239 DAT, and in sorghum straw at 367 DAT. No residues >0.01 ppm of fipronil or MB45950 were detected in any crop.

Based on these results, the appropriate PBI for root, leafy and legume vegetables is 120 days. However, as quantifiable residues were observed in sorghum straw, rotational crop tolerances are

required for small grains and all other crops. The required number of field trials required to set rotational crop tolerances is the same as that required to establish primary crop tolerances.

The registrant has submitted the results of 12 field trials for wheat planted as a rotational crop. Trials using corn as the primary crop were performed in Regions 2 (1 trial), 5 (4 trials) and 6 (1 trial). Trials using cotton as the primary crop were performed in Regions 2 (1 trial), 4 (1 trial) and 8 (4 trials). Wheat was planted after corn and cotton between 2-5 months after application of soil with fipronil. All regions for which wheat trials are required were adequately represented except Regions 7 and 11. As region 11 contains significant acreage of potato, additional wheat residue data would normally be required, however, since in the field accumulation trials using cotton as the primary crop, the rate was 2x proposed rate for potato use and since no residues were found in the grain of rotated wheat (human food item), no additional field accumulation in rotational crops are needed. More field accumulation in rotational crops may be requested in future should additional uses are proposed.

The total of fipronil + metabolites MB46136 and MB45950 + photodegradate MB46513 were a maximum of 0.017 ppm in forage, 0.024 ppm in hay and 0.024 ppm in straw. No residues ≥LOQ were detected in grain. Based on these results, the appropriate tolerances for indirect/inadvertant residues of fipronil + metabolites MB46136 and MB45950 + photodegradate MB46513 are 0.005 ppm on wheat grain, 0.02 ppm on forage, 0.03 ppm on hay and 0.03 ppm on straw. A revised Section F is required. The available rotational crop data support PBIs of 2 months for wheat and 4 months for root, leafy and legume vegetables. Rotation to all other crops (except registered crops) should be prohibited.

4.2.1.j. International Harmonization of Tolerances

There are no Codex, Canadian, or Mexican maximum residue limits (MRLs) established for fipronil + metabolites MB46136 and MB45950 + photodegredate MB46513 on the commodities included in this request. Thus, harmonization is not an issue. A copy of the International Residue Limits Status (IRLS) sheet is attached to this risk assessment (Attachment 4).

4.2.2. Drinking Water

The HED Metabolism Committee determined that the residues of concern in drinking water are fipronil + metabolites MB46136 and MB45950 + photodegredate MB46513. Therefore, EFED provided a comparative drinking water assessment for the following proposed and registered fipronil uses: 1.) in-furrow, at plant use on sweet potato/potato; 2.) Section 18 for in-furrow, at plant use on rutabagas and turnips in Oregon; 3:) in-furrow, at plant corn; corn seed treatment at 30 inch and 15 inch row spacings; 4.) onion seed treatment; 5.) in-slit treatment for mole cricket; 6.) broadcast application for fire ants; and 7.) broadcast application of Texas leaf-cutter bait (DP Barcode: D318481 & D318373, J. Hetrick, in process). The drinking water assessment is based on screening-level models because available monitoring data represent cancelled fipronil uses (i.e., rice) or are not targeted to all fipronil use areas. The acute, short + long-term and chronic dietary risk analyses incorporated water concentration estimates from the onion seed treatment scenario due to the stability of these numbers. Based on

the Tier 1 screening model SCI-GROW, acute drinking water EEC in shallow ground water on highly vulnerable sites is not likely to exceed **0.006909 ppb** in acute scenarios and **0.003063 ppb** in chronic scenarios.

4.2.2.a. Environmental Fate Assessment

Fipronil is stable ($t_{1/2}$ >30 days) in pH 5 and pH 7 buffer solution and hydrolyzes slowly ($t_{1/2}$=28 days) in pH 9 buffer solution. The major hydrolysis degradate is RPA200766 (5-amino-3-carbamoyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoro-methanesulfinyl pyrazole. Photodegradation of fipronil is a major route of degradation (photodegradation in water half-life=3.63 hours) in aquatic environment. In contrast, fipronil photodegradation on soil surfaces (dark control corrected half-life=149 days) does not appear to be a major degradation pathway. Major photolysis products of fipronil are MB46513 and RPA104615 (5-amino-3-cyano-1-(2,6-dichloro-4-trifluoro methyl phenyl) pyrazole-4-sulfonic acid). The chemical degradation of fipronil appears to be dependent predominately on photodegradation in water and, to a lesser extent, on alkaline-catalyzed hydrolysis.

Fipronil degradation in terrestrial and aquatic systems appears to be controlled by slow microbially-mediated processes. In aerobic mineral soil, fipronil is moderately persistent to persistent ($t_{1/2}$= 128 to 300 days). Major aerobic soil degradates (>10% of applied of fipronil) are RPA200766 and MB46136. Minor degradates (<10% of applied fipronil) are MB45950 and MB46513. Fipronil also is moderately persistent (anaerobic aquatic $t_{1/2}$ = 116-130 days) in anoxic aquatic environments. Major anaerobic aquatic degradates are MB45950 and RPA200766. Supplemental aerobic aquatic metabolism data indicate that fipronil degradation ($t_{1/2}$=14 days) is rapid in aquatic environments with stratified redox potentials. These data contradict the longer fipronil persistence reported in anaerobic aquatic and aerobic soil environments.

Conclusions regarding the environmental fate of fipronil degradates, except MB46513, are more tentative because they are based on a preliminary review of interim data not a formal evaluation of a fully documented study report. Since discernable decline patterns for the fipronil degradates were not observed in metabolism studies, the degradates are assumed to be persistent ($t_{1/2}$=700 days) to microbially mediated degradation in terrestrial and aquatic environments. However, the fipronil degradate, MB46136, rapidly photodegrades ($t_{1/2}$=7 days) in water.

Fipronil degradates have relatively low potential mobility because of a moderate to high sorption affinity to soil. The high sorption affinity of fipronil degradates is expected to limit movement into ground and surface water.

Table 9: Environmental Fate Data for Fipronil Degradation Products			
Fate Parameter	**MB 46136**	**MB 46513**	**MB 45950**
Mean Koc	4208 mL/g	1290 mL/g	2719 mL/g
Aerobic Soil Metabolism Half-life	700 days	660 days	700 days
Aqueous Photolysis Half-life	7 days	Stable	Stable
Hydrolysis Half-life	Stable	Stable	Stable
Aquatic Metabolism Half-lives	1400 days	1320 days	1400 days
Water Solubility	0.16 mg/L	0.95 mg/L	0.1 mg/L
% of Fipronil Application Rate	23.9	0.96	4.9
References	RP# 201555 ACD/EAS/Im/255 Theissen 10/97	MRID 44262831 44262830 Theissen 10/97	RP 201578 Theissen 10/97

4.2.2.b. Surface Water Assessment

PRZM (3.12 beta) and EXAM (2.97.5) using PE4V01.pl (August 13, 2003) modeling was conducted using standard scenarios which are representative of high runoff areas or specific use areas. EFED also conducted surface water modeling for the individual degradation products including MB 46513, MB 46136 and MB45950. The modeling was conducted assuming the maximum daily conversion efficiency for the compound was represented by the maximum percentage formed in the environmental fate laboratory studies. Because the fipronil degradation products are formed through abiotic or biotic degradation pathways in soil and water, the degradation products were assumed to have a 100% application efficiency on the soil surface. There was no correction for molecular weight because the molecular weights of fipronil and degradation products are similar. Application rates are based on a fipronil equivalence basis. By adding the 1 in 10 year peak concentration for fipronil and it's metabolites and the 1 in 10 year annual average concentrations for the onion seed treatment scenario, the acute value is 0.006909 ppb and the chronic is 0.003063 ppb (DP Barcode: D318481 & D318373, J. Hetrick, in process).

4.2.2.c. Ground Water Assessment

Ground water concentrations were estimated using SC2.3 (July 29, 2003). Aerobic soil metabolism rate, Koc, and application rate (lbs/A) for fipronil and its degradation products were derived from PRZM/EXAMS inputs. The proposed use on onion seed had the highest predicted

concentration (80.05 ng/L) in ground water. Low concentrations of degradation products were estimated because of their high soil carbon sorption coefficients and low formation efficiencies (DP Barcode: D318481 & D318373, J. Hetrick, in process).

4.2.2.d Drinking Water Assessment

PRZM/EXAMS simulations of the various registered and proposed uses of fipronil show a range of estimated concentrations in drinking water. The highest water numbers for the proposed and established uses come from the onion seed treatment scenario and these were used to estimate drinking water concentrations. Drinking water EEC on highly vulnerable sites is not likely to exceed **0.006909 ppb** in acute scenarios and **0.003063 ppb** in chronic scenarios (DP Barcode: D318481 & D318373, J. Hetrick, in process).

4.2.3. Dietary Exposure and Risk Analyses

HED conducts dietary (food only) risk assessments using DEEM™, which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, one-day consumption data are summed and a food consumption distribution is calculated for each population subgroup of interest. The consumption distribution can be multiplied by a residue point estimate for a deterministic exposure/risk assessment, or be used with a residue distribution in a probabilistic type risk assessment. Acute exposure estimates are expressed in mg/kg bw/day and as a percent of the aPAD. For chronic risk assessments, residue estimates for foods or food-forms of interest are multiplied by the average consumption estimate of each food/food-form of each population subgroup. Chronic exposure estimates are expressed in mg/kg bw/day and as a percent of the cPAD.

4.2.3.a. Acute Dietary Exposure Analysis

A Tier 1 acute dietary risk assessment was performed assuming tolerance-level residues, 100% CT and a drinking water (acute) modeled concentration of 0.006909 ppm. Default processing factors were used for all commodities except for potato, flakes and potato, chips, both of which are dried potato commodities. These are usually given the default processing factor of 6.5. HED determined, via residue data, that the processing factors for these commodities are actually <1. Using a processing factor of 1 allows for a more conservative estimate of the acute dietary exposure and risk. For acute dietary risk, HED's level of concern is >100% aPAD. Dietary exposure estimates for the U.S. population and other representative subgroups are presented in Table 10.

Table 10. Summary of Results from Acute DEEM™ Analysis at 95th Percentile		
Subgroups [1]	**Exposure (mg/kg/day)**	**% aPAD**
U.S. Population	0.002458	9.8
All infants (<1 year old)	0.003436	14
Children (1-2 years old)	0.006303	25
Children (3-5 years old)	0.004571	18
Children (6-12 years old)	0.002954	12
Youth (13-19 years old)	0.001889	7.6
Adults 20-49 years old.	0.001460	5.8
Females (13-49 years old)	0.001410	5.6
Adults (50+ years old)	0.001211	4.8

[1] HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys, (e.g., non-nursing infants, etc.). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (e.g., all infants, females, 13-50 years, etc.).

The results of the acute analysis indicate that the estimated acute dietary risk associated with the existing and HED recommended uses of fipronil is below HED's level of concern (<100% aPAD).

4.2.3.b. Chronic Dietary Exposure Analysis

A partially-refined analysis was performed using ARs from field trial data, processing factors, %CT information from the last fipronil dietary analysis (DP Barcode: D248827, S. Levy, 02/20/2001) and a new drinking water (chronic) modeled concentration of 0.003063 ppm. New AR data for potato and sweet potato commodities, as well as processing factors, were provided by HED (DP Barcode: D313293 & D318283, M. Sahafeyan, 08/05/2005). Projected market share data for onions, potatoes and sweet potatoes were provided by BEAD (from email, Halvorson). Processing data for wheat RACs are not available at this time; therefore the wheat, grain tolerance was used for all wheat commodities. HED also determined that existing tolerances on livestock should been maintained. For chronic dietary risk, HED's level of concern is >100% cPAD. Dietary exposure estimates for the U.S. population and other representative subgroups are presented in Table 11.

The following ARs provided by HED and projected market share data provided by BEAD, were used in the Tier 2 chronic analysis for the expected residues of fipronil and its metabolites:

Commodity	AR	%CT
Onion (dry bulb), shallot (dry bulb)	0.030 ppm	42
Potatoes (tuber)	0.028 ppm	39
Potatoes (chip)	0.023 ppm	39
Potatoes (flakes)	0.026 ppm	39
Potatoes (wet peels)	0.390 ppm	39
Sweet Potatoes	0.028 ppm	56

Table 11. Summary of Results from Chronic DEEM™ Analysis.

Subgroups [1]	Exposure (mg/kg/day)	% cPAD
U.S. Population	0.000095	47
All infants (<1 year old)	0.000239	**120**
Children (1-2 years old)	0.000156	78
Children (3-5 years old)	0.000142	71
Children (6-12 years old)	0.000094	47
Youth (13-19 years old)	0.000070	35
Adults (20-49 years old)	0.000083	42
Females (13-50 years old)	0.000081	40
Adults (50+ years old)	0.000101	51

[1] HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys. (e.g., non-nursing infants, etc.). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (e.g., all infants, females, 13-50 years, etc.).

The results of the chronic analysis indicate that the estimated **chronic dietary risk associated with the existing and HED-recommended uses of fipronil is above HED's level of concern** (<100% cPAD).

4.2.3.c. Cancer Dietary Exposure Analysis

Fipronil has been classified as a "Group C" chemical (possible human carcinogen) by the HED CPRC (document dated 7/18/95). The HIARC determined that cancer dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the DEEM™ chronic exposure analysis using the RfD; therefore, a cancer dietary exposure analysis was not performed.

4.3. Occupational/Residential Exposure

4.3.1. Summary of Use Patterns and Formulations

Fipronil is currently registered for use on cats and dogs for flea control (various formulations) and on turf to control fire-ants (various formulations). Tolerances are established on many raw agricultural commodities. Registered residential uses of fipronil have been assessed previously by HED and are referenced below (see "Residential Exposure and Risk"). In this document, fipronil uses that could result in residential exposure have been summarized for aggregate risk assessment.

BASF chemical company has requested registration of the insecticide fipronil for use on onion seed (dry bulb), shallot seed (dry bulb), potatoes, sweet potatoes, turnips and rutabagas in Oregon, and on turf for control of leaf cutter ants. Several products are proposed for these uses. Products and the proposed use patterns are described below. See Table 12 for a summary of the proposed use patterns.

Table 12. Summary of Directions for Use of Fipronil.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Onion Seed (dry bulb), Garlic Seed (dry bulb), Shallot Seed (dry bulb)						
Seed treatment using any equipment capable of applying viscous liquid products	Regent® TS [7969-223]	0.025 lb ai/ lb of seed	NA	NA	NA	Treated seed must have unnatural appearance or color to indicate that the seed is treated.
Tuberous and corm vegetables subgroup (Crop Subgroup 1-C)						
1 in-furrow applic. at planting by liquid spray system	Regent® 4 SC [7969-207]	0.09-0.10 lb ai/A	1	0.10 lb ai/A	90	Do Not apply in row spacing less than 30 inches.

Proposed Uses

Based upon the proposed use patterns, HED expects the most highly exposed occupational pesticide handlers are likely to be:

1) seed treatment workers (loader/applicators, sewers, baggers)
2) planters planting treated seed
3) handlers mixing/loading for groundboom application

4) applicator using open-cab ground-boom spray equipment for in-furrow treatment
5) handlers performing broadcast application for leaf cutter ant control

For some of the application methods, the same individual might perform multiple activities. The HED Science Advisory Council for Exposure (ExpoSAC) draft Standard Operating Procedure (SOP) (29 March 2000) directs that although the same individual may perform all tasks, in some cases they shall be assessed separately.

The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the data available for monitoring of these two activities separately. These exposure scenarios are outlined in the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of personal protective equipment (PPE) for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline" PPE, that includes a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves as well as for "baseline" PPE **plus** the use of protective gloves or other PPE as might be necessary. The proposed product label involved in this assessment directs applicators and other handlers to wear long-sleeved shirt, long pants and shoes plus socks.

On October 5, 2000, the HED HIARC met to assess the hazard data base for fipronil (TXR NO. 014400, *FIPRONIL: THIRD REEVALUATION - Report of the Hazard Identification Assessment Review Committee*, M. Copley, 12/06/2000). Relative to this assessment, the HIARC an endpoint for use in short-term (1 - 30 days) and intermediate-term (30 days-6 months) dermal risk assessment from a 21-day dermal toxicity study in rabbits with a No Observable Adverse Effect Level (NOAEL) of 5 mg/kg/day based on decreased body weight gain and food consumption in male and female rabbits observed at 10 mg/kg/day (the lowest-observed effect level or LOAEL). A dermal absorption factor is not needed since a dermal toxicity study is the basis for the dermal endpoint.

An endpoint for use in short-term and intermediate-term inhalation risk assessment was also identified. The inhalation endpoint was chosen from a developmental neurotoxicity study in rats

in which a decrease in group mean pup weights during lactation, and significant increase in time of preputial separation in males (dietary) were observed at the LOAEL of 0.90 mg/kg/day. For inhalation exposure, HED assumes 100 % absorption.

Fipronil has been classified by the HED CPRC as a Group C - Possible Human Carcinogen based on increases in thyroid follicular cell tumors in both sexes of the rat. The HIARC determined that cancer dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the DEEM™ chronic exposure analysis using the RfD. Therefore, a non-dietary cancer risk assessment was not performed.

4.3.2. Occupational Exposure Assessment

An MOE of 100 is adequate to protect occupational pesticide handlers. For a summary of estimated exposures and risks, see Table 13.

Table 13. Handler Exposure and Risk from Proposed Uses of Fipronil

Unit Exposure[1] mg a.i./lb handled	**Applic. Rate[2]**	**Units Treated[3] Per Day**	**Average Daily Dose[4] mg a.i./kg bw/day**	MOE[5]
Onion/Shallot Seed Treatment: Multiple Activities[6]				
Dermal: 0.042 Inhalation: 0.0016	0.024 lb ai/ lb seed	5,000 lbs seed	Dermal: 0.073 Inhalation: 0.0028	**Dermal: 69** **Inhalation: 18**
Onion/Shallot Seed Planters				
Dermal: 0.25 Inhalation: 0.0034	0.024 lb ai/ lb seed	320 lbs seed	Dermal: 0.028 Inhalation: 0.00038	Dermal: 180 Inhalation: 130
Mixer/Loader -Liquids - Open Pour For Treatment to Potatoes, Sweet Potatoes				
Dermal: SLNG 2.9 HC SLWG 0.023 MC Inhalation: 0.0012 HC	0.13 lb a.i./A	80 A	Dermal: NG 0.43 WG 0.0034 Inhalation: 0.00018	**Dermal:** **NG 12** WG 1,500 Inhalation: 280
Applicator - Ground-boom - Open Cab Treatment to Potatoes, Sweet Potatoes - Followed by Soil Incorporation				
Dermal: SLNG 0.014 HC SLWG 0.014 MC Inhalation: 0.00074 HC	0.13 lb a.i./A	80 A	Dermal: NG 0.0021 WG 0.0021 Inhalation: 0.00011	Dermal: NG 2,400 WG 2,400 Inhalation: 450
Applicator - Push Type Granular Spreader Broadcast Bait to Control Leaf Cutter Ant				

Dermal SLNG 2.9 LC SLWG No data Inhalation: 0.0063 HC	0.0029 lb a.i./A	5 A	Dermal: NG 0.0006 WG no data Inhalation: 0.000001	Dermal: NG 8,400 WG no data Inhalation: 38,000

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. SLNG = Dermal Single Layer Work Clothing **No Gloves**; SLWG = Dermal Single Layer Work Clothing **With Gloves**; Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Applic. Rate. = Taken from appropriate fipronil labels.
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; SOP No. 9.1. Science Advisory Council for Exposure: Revised 5 July 2000;
4. Average Daily Dose = Unit Exposure * Applic. Rate * Units Treated ÷ Body Weight (70 kg).
5. MOE = Margin of Exposure = No Observable Adverse Effect Level (NOAEL) ÷ ADD. Short-term and intermediate-term dermal NOAEL = 5 mg a.i./kg bw/day. Short-term and intermediate-term inhalation NOAEL = 0.05 mg/kg/day.
6. "Multiple Activities" for seed treatment represents the worker who would perform all three activities: load/apply fipronil to the seed, bag the treated seeds and sew the bags (as a high end estimate).

All occupational risk estimates are below HED's level of concern (MOE>100) *provided workers wear protective gloves* when handling fipronil, except for the estimates of risk to seed treatment workers (MOEs of 69 and 18 for dermal and inhalation risk, respectively).

HED has received information from OPP's Biological and Economic Analysis Division (BEAD; personal communication from D. Brassard, 8/8/05) suggesting that no more than 4,000 - 5,000 lbs (enough to treat 1000 acres) would be handled by a single facility. Further, BEAD stated that it is likely that much less than 5,000 lbs is treated per day. This estimate is based on data from California, where about 38,000 acres of onion are planted per year.

The seed treatment results can be considered conservative due to the exaggerated amount of seed treated, and since they are for workers performing all seed treatment tasks (applying, bagging and sewing). Further clarification on this issue may be forthcoming from IR-4.

However, since the estimates of risk for seed treatment exceed HED's level of concern (MOEs of 69 and 18, for dermal and inhalation exposure, respectively), HED welcomes the petitioner's input regarding the amount of seed treated per day.

4.3.2.a. Worker Post-Application Exposure Assumptions and Assessment

In-Furrow Uses (Potatoes, Sweet Potatoes)
Dermal post-application occupational exposure based on the in-furrow uses of fipronil are expected to be negligible as the soil is normally not contacted after incorporation.

Onion/Shallot Seed Treatment Use
The post-application use scenario for seed treatment uses consists of the grower purchasing bags of treated seed, placing the seed in the hopper and planting the seed in the field. Estimated risks resulted in MOEs of 180 and 130 for dermal and inhalation risk, respectively. Planting of treated seed is not a standardized practice, but HED believes that the estimates presented herein are conservative and may even be an over-estimate of exposure and risk.

Leaf-Cutter Ant Use on Turf
For the leaf-cutter ant (dry broadcast use), fipronil is applied as a dry granule. Relative to the other proposed uses, the rates of application are very low for the 0.003% medium granular formulation. Dermal absorption is estimated by HIARC to be 1% (dermal absorption was not used in risk calculations because the dose and endpoint for dermal risk assessment were derived from a dermal study).

4.3.2.b. REI

The proposed Regent 4 SC label states, "Do not enter or allow worker entry into treated areas during the REI of 0 hours." **This language is not supported by the Worker Protection Standard regulation.**

For Regent 4 SC, due to the nature of the use pattern (soil incorporation), the REI is based on the acute toxicity of the active ingredient, fipronil. Since fipronil falls into Acute Toxicity Category III for dermal and eye irritation and Category IV for skin irritation, **the REI shall be 12 hours. RD should ensure that the proper REI appear on Regent 4 SC labels.**

The following language should be stated on the Regent 4 SC label in the box "Agricultural Use Directions:"

> *Exception: if the product is soil-injected or soil-incorporated, the Worker Protection Standard, under certain circumstances, allows workers to enter the treated areas without restriction if there will be no contact with anything that has been treated.*

The proposed BES 100 Insecticide label carries an 8 hour REI.

4.3.2.c. Incident Reports

There are incident reports through December 1996 (DP Barcode: D233461, V. Dobozy, 4/1/97) and from March 17, 1997 to April 13, 1998 (DP Barcode: D241621, V. Dobozy, 4/29/98) for companion animals. However, no incidents of human exposure have been reported.

4.3.3. Residential Exposure

4.3.3.a. Residential Exposures and Assumptions - Leaf Cutter Ant Use

The granular product for control of leaf cutter ants is intended for direct broadcast to affected turf areas, which may include residential and public areas where adults and children could come into contact with fipronil. The estimates reported in Table 13 represent occupational and residential exposure to adult handlers. The estimated MOEs for handlers are 8,400 and 38,000 for dermal and inhalation risk, respectively. Also, HED previously assessed the use on fire-ants using a higher application rate for homeowners using a drop spreader, which is a method of application with much higher exposure compared to the solid broadcast spreader. Therefore, HED does not

expect estimated risks for residential handlers using the leaf-cutter ant product (BES 100 Insecticide) to exceed HED's level of concern.

Previously, HED assessed risks from a similar granular fipronil product used for control of fire-ants (*Occupational & Residential Human Exposure and Risk Assessment/ Characterization for Eight Fipronil Products Used Against Fire-ants and Other Pests*, DP Barcode: D244048 M. Dow. 10/24/2000. For the previously assessed fire-ant use, chemical-specific data were available for risk assessment. These data are applicable to the proposed use for leaf cutter ant control since the use pattern is similar (broadcast granular).

The registrant has submitted a dislodgeable foliar residue (DFR) study on granular fipronil treated turf (MRID No. 44506901). Data from this study suggest that fipronil cannot be dislodged from turf after a single application of granules. Therefore, dermal post-application exposure assessments are not presented for residential turf.

However, residential risk to toddlers was assessed based on the proposed use on residential turf. Two post-application exposure scenarios were assessed: 1) post-application toddler exposure from the incidental ingestion of pesticide granules and 2) post-application toddler exposure from incidental ingestion of treated soil.

The calculations of risk are based on HED guidance (Standard Operating Procedures for Residential Exposure Assessments. 12/18/1997. pp 28-30.). The estimates of toddler risk are considered conservative estimates of oral exposure due to the many default assumptions (i.e., soil ingestion rate).

4.3.3.b. Residential Exposures and Assumptions - Pet Products

Fipronil is currently registered for use on pets. An assessment of exposures to the pet products was conducted (DP Barcode: D246176, G. Kramer *et al.*, 5/22/1998). Levels of concern were not exceeded for residential applicators or for post-application dermal exposure to toddlers. Exposure and risk estimates from the previous assessment are summarized below.

The probability of applying fipronil to pets and applying fipronil to control turf pests on the same day is considered to be negligible. Therefore, for aggregate risk assessment, exposure from pet and turf treatments should not be combined.

The residential exposure is assessed for the Frontline® pet products. The following three fipronil products are conditionally registered by Aventis for flea and tick control: Frontline® Spray Treatment (65331-1), Top Spot® for Cats (65331-2) and Dogs (65331-3). Fipronil is used to control fleas and ticks on dogs and cats and is applied as a Ready-to-Use (RTU) pump spray (Frontline®) to the fur of the animal or as a RTU, pour-on, spot treatment made along the back of the animal between the shoulder blades (Top-Spot®). Frontline® may be applied by both professional groomers and homeowners. The dosage per pound of the animal's body weight is approximately 5 mg. Repeated applications if necessary may be made once every one to three months during flea or tick season.

Aventis has submitted exposure studies to support the use of fipronil on dogs and cats for the control of fleas and ticks. There are two studies addressing the application of fipronil: 1) Dermal and Inhalation Exposure of Commercial Pet Groomers During Application of Frontline® Spray Treatment (MRID No. 44433302), and 2) Dermal Exposure of Commercial Pet Groomers During the Application of Frontline® and Top Spot® (MRID No. 44433303). Aventis has also submitted four studies to address the dislodgeable residues of fipronil from dogs and cats following the application of both the spray treatment and the spot treatment (MRID Nos. 44433301-09). HED reviewed these studies and assessed the potential residential exposures based on the data that was submitted (DP Barcode: D246176, G. Kramer, *et. al.*, 5/22/1998).

Based on the review of these studies, the dermal and inhalation exposures for residential applicators were estimated to be **0.003** mg/kg/day and **0.00000178** mg/kg/day, respectively. The non-dietary, oral (hand-to-mouth) was estimated to be no greater than **0.00003** mg/kg/day. The post-application dermal exposure for toddlers was estimated to be **0.001** mg/kg/day.

Table 14 summarizes the exposure estimates for homeowner and toddler exposure to fipronil in Frontline® pet products. These exposure estimates represent exposure to the pet immediately after application of spot or spray treatment. The MOEs were calculated from the exposure estimates obtained from the review of previously submitted studies (DP Barcode: D246176, G. Kramer, *et. al.*, 5/22/1998). Since more exposure is expected from the Frontline® Spray product, exposure estimates for the Frontline® Spot application are not provided. Exposure to the Frontline® Spray product represents the worst case for all residential scenarios.

In addition, exposure to the photodegradate MB46513 was not assessed due to minimal potential for exposure to both of the registered residential use products. Residential exposure to the photodegradate is not expected while spraying or handling a recently treated pet as these are brief periods usually occurring indoors. Post-application exposure to the degradate is also not expected due to the products reportedly strong affinity to the sebum and epidermis of pets.

Table 14. Estimated Risks for the Use of Fipronil to Control Fleas and Ticks on Pets

Receptor	Short-Term Dermal MOE [1]	Intermediate-Term Dermal MOE [1]	Short- and Intermediate-term Inhalation MOE [1]	Non-Dietary Oral MOE [1]
Homeowner spray: application exposure	1,700	1,700	28,000	--
Toddler: post-application exposure	5,000	5,000	--	3,300

[1] MOE = NOAEL/Exposure (dermal NOAEL = 5 mg/kg/day, inhalation = 0.05 mg/kg/day, short- and intermediate-term incidental oral = 0.1 mg/kg/day).

MOEs are 1,700 and greater for all handling activities associated with the use on pets. MOEs are 3,300 and greater for all post-application exposures associated with the use on pets. Therefore, all residential exposures are below HED's level of concern.

4.3.3.c. Residential Exposure and Assumptions - Fire Ant Products

Previously, HED assessed several granular products intended for use on residential turf as well as a RTU trigger pump spray formulation for use as a perimeter (outside only) treatment around residences (DP Barcode: D244048, M. Dow and D. Vogel,10/24/2000). Table 15 below contains assessments of homeowner exposure from the registered uses as a granule and a RTU trigger pump spray.

Table 15. Handler Exposure from Fire-Ant Uses.

Job Function and Formulation	Unit Exposure [1] mg ai/lb ai handled	Data Confidence	Units/ Day [2]	AR [3] lb ai/unit	ADD [4] derm mg ai/kg	ADD [4] inhal bw/day	MOE [5] derm	MOE [5] inhal
Homeowner Granular dispersed/hand	430 derm 0.467 inhal	med med	0.5 A[a]	0.000023 lb ai/A	8.6^{-5}	9.3^{-8}	>58K	>500K
Homeowner Belly-grinder open pour MLA	110 derm 0.062 inhal	med high	0.5A [a]	0.000023 lb ai/A	2.2^{-5}	1.24^{-8}	>200K	>4M
Homeowner Drop Spreader open pour MLA	3.0 derm 0.0063 inhal	low high	0.5 A[a]	0.000023 lb ai/A	5.7^{-7}	1.2^{-9}	>8M	>41M
Homeowner 0.0143% G Drop Spreader	3.0 derm 0.0063 inhal	low high	0.5 A[a]	0.024 lb ai/A	6.0^{-4}	1.3^{-6}	>8K	>38K
Homeowner 0.05% RTU	220 derm 2.4 inhal	med med	24 fl[b] oz/day	3.3^{-5} lb ai/fl oz	2.9^{-3}	3.2^{-5}	>1.7K	>1.5K

1 Unit Exposures for homeowner applications are taken from "DRAFT Standard Operating Procedures (SOPs) for Residential Exposure Assessments," Dec. 18, 1997, p B-3, B-4, B-5, B-6 and B-16.

2 a. Draft SOPs for Residential Exposure Assessments, 12/18/97, p 12; b. Proposed label for H&G 61748A fipronil insecticide RTU Spray.

3 Proposed labels for Chipco Banish File Symb. 264-LIG; Chipco Choice File Symb. 264-LLN; Chipco 61748; End User Fipronil File Symb 264-LOE; Chipco 61748A Service Fipronil File Symb 264-LON; H&G 61748A; Fipronil Insecticide File Symb. 264-LOL; H&G 61743A RTU Insecticide Spray File Symb. 264-LOT; Chipco 61442A Imported Fire-ant Bait.

4 ADD = Unit Exposure x AR x Unit/Day x 1/BW (60 kg for homeowner).

5 MOE = NOAEL/ADD

4.3.3.d. Toddler Incidental Ingestion of Pesticide Granules

HED believes that if a toddler were to be exposed to fipronil residues on treated turf, the exposure to granules is most likely to be "episodic", that is, a one time occurrence and not likely to be repeated. Therefore, to estimate risk, HED used the acute dietary NOAEL of 2.5 mg/kg bw/day from an acute neurotoxicity study with the LOAEL of 7.0 mg a.i./kg bw based on decreased hind leg splay in males at 7 hours.

Calculations of toddler risks from ingestion of granules are presented below.

For toddlers, the Potential Dose Rate (PDR)[1] (mg/day) may be calculated as:

$$PDR = IgR \times F \times CF1$$

where:

IgR = ingestion rate of dry formulation (0.3 g/day)
F = fraction of ai in dry formulation (0.003% = 0.00003; unitless)
CF1 = weight unit conversion factor to convert g units in the ingestion rate value to mg for daily exposure (1000 mg/g).

Thus the PDR for the residential granule formulation =
0.3 g/day x 0.00003 x 1000 mg/g = 0.009 mg/day.

The PDR_{norm} = the PDR/bw (15 kg for toddler) = 0.009 mg/day ÷ 15 = 0.0006 mg/kg/day

MOE = $NOAEL/PDR_{norm}$ = 2.5 mg ai/kg bw/day ÷ 0.0006 mg/kg/day = **4,200**.

4.3.3.e. Toddler Incidental Soil Ingestion

HED believes that toddler's incidental soil ingestion might occur on a repeated basis. Toddlers may ingest soil as a result of normal hand to mouth behavior, and, thus, possibly ingest pesticide that has been applied to the soil. Therefore, to estimate risk, HED used the short-term incidental oral LOAEL of ≤ 0.1 mg a.i./kg bw/day which is based on a rabbit developmental toxicity study where the maternal effects included decreased body weight gain and decreased food efficiency. Due to the lack of NOAEL, HED's level of concern is an MOE of 300 or more.

Calculations of toddler risks from ingestion of soil are presented below.

The Post-Application Potential Dose Among Toddlers from Incidental Ingestion of Soil from Pesticide-Treated Residential Areas may be calculated as:

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[1] Postapplication Potential Dose Among Toddlers from the Ingestion of Pesticide Pellets or Granules from Treated Areas in: Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments, p 19, 18 DEC 97

$PDR_t = SR_t * IgR * CF_1$

where PDR = Potential Dose Rate on day "t" (mg/day)
SR_t = soil residue on day "t" (µg/g)
IgR = ingestion rate of soil (100 mg/day)
CF_1 = Weight unit conversion factor to convert µg of residues on soil to grams to obtain mg/day (1E-6g/µg)

$SR_t = AR * F * (1 - D)^t * CF2 * CF3 * CF4$

where AR = application rate (0.00288 lb a.i./Acre)
F = fraction of a.i. available in uppermost cm of soil (fraction/cm)
D = fraction of residue that dissipates daily (unitless)
t = post-application day on which exposure is being assessed
CF2 = weight unit conversion factor to convert the lbs a.i. in the application rate to µg for the soil residue value (4.54E8 µg/lb)
CF3 = area unit conversion factor to convert the surface area units (ft^2) in the application rate to cm^2 for the SR value (1.08E-3 ft^2/cm^2 or 2.47E-8 acre/cm^2 if the application rate is per acre)
CF4 = volume to weight unit conversion factor to convert the volume units (cm^3) to weight units for the SR value (U.S. EPA, 1992) (0.67 cm^3/g soil)

Therefore, the application rate of 0.00288 lb a.i./A ÷ 43,560 ft^2/A = 6.6×10^{-8} lb a.i./ft^2

$SR_t = AR * F * (1 - D)^t * CF2 * CF3 * CF4$
6.6^{-8} lb a.i./ft^2 * 1.0/cm * $(1 - D)^0$ * 4.54^8 µg/lb * 1.08^{-3} ft^2/cm^2 * 0.67 cm^2/g = 0.022 µg/g

$PDR_t = SR_t * IgR * CF1$
0.022 µg/g * 100 mg/day * $(1*10^{-6})$ g/µg = 2.1×10^{-6} mg/day

Normalized to toddler body weight (15 kg)
$PDR_{t\text{-norm}} = PDR_t/bw = 2.1^{-6}$ mg day ÷ 15 kg bw = 1.0^{-7} mg a.i./kg bw/day

MOE = NOAEL ÷ PDR_{norm} =
0.1 mg a.i./kg bw/day ÷ 1.2^{-6} mg a.i. kg bw/day = **1 million**

For soil ingestion, HED's level of concern is 300. Therefore, based on conservative, screening level assumptions, the MOE for episodic ingestion of granules is 4,200 and the MOE for incidental soil ingestion is 1,000,000, HED's levels of concern are not exceeded for toddlers as described above.

4.3.4. Aggregate Residential Exposure

Fipronil is currently registered for use on pets. An assessment of exposures to the pet products was conducted (DP Barcode: D246176, G. Kramer, *et al.*, 5/22/1998). The probability of

applying fipronil to pets and applying fipronil to control turf pests on the same day is considered to be negligible. Levels of concern were not exceeded for residential applicators or for post-application dermal exposure to toddlers.

Based on the existing and proposed uses, the previously-assessed pet uses result in the highest estimated handler risks (see Table 13). For post-application risk, the estimates provided above for the proposed use on pets should be used to estimate risk to toddlers (incidental ingestion of granules and soil). Adult post-application risk is considered negligible, as noted in Table 13, due to the high MOE for inhalation exposure.

4.3.5. Photodegradate

The fipronil photodegradate MB46513 is not considered pertinent to this assessment. In a 1/26/98 memorandum (EFED Section 3 Decision for fipronil on Rice Seed; DP Barcode: D235912; Fipronil Rice Team, EBB 1 to M. Johnson, Insecticides Branch, Registration Division), EFED characterized the metabolite as follows: "Fipronil is relatively persistent and immobile in terrestrial environments. Fipronil dissipation appears to be dependent on photodegradation in water, microbially mediated degradation and soil binding. Since fipronil and its degradates have a moderate to high sorption affinity to soil, it is likely soil sorption will control residue movement into ground and surface waters. Photodegradation of fipronil **is a major route of degradation...in the aquatic environment....** In contrast, fipronil photodegradation on soil surfaces **does not appear to be a major pathway."**

Kramer *et al.* (DP Barcode: D246176, 5/22/1998) determined that the photodegradate need not be assessed relative to the uses on pets. With the exception of the RTU product, fipronil is applied as a dry material to non-aqueous substrates; therefore, it is not considered pertinent to this assessment.

4.4. Non-Occupational Off-Target Exposure

This assessment for fipronil reflects the Agency's current approaches for completing residential exposure assessments based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines*, the *Draft: SOPs for Residential Exposure Assessment*, and the *Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment* presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available. This will include expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from other sources already not addressed such as from spray drift; residential residue track-in; exposures to farm worker children; and exposures to children in schools.

5.0. RISK ASSESSMENTS AND RISK CHARACTERIZATION

Aggregate exposure risk assessments were performed for acute and chronic aggregate exposure (food + drinking water) and short/long-term aggregate exposure (food + drinking water + residential use). Since HED was able to provide a drinking water assessment for the proposed and registered uses of fipronil, DWLOCs were not calculated. The dietary risk analysis incorporated water concentration estimates from the onion seed treatment scenario for both the acute and chronic dietary analysis. A cancer aggregate risk assessment was *not* performed because HIARC determined that cancer dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the chronic exposure assessment.

5.1. Acute Aggregate Risk (food + drinking water)

Acute aggregate risk estimates are below HED's level of concern. A partially refined acute analysis was performed assuming tolerance level residues and that 100% of each crop was treated for onions and shallots at 0.03 ppm, potato and sweet potatoes at 0.03 ppm, wheat, grain at 0.005 ppm and water (acute) at 0.001036 ppm. Default processing factors were used for all commodities except for potato, flakes and potato, chips, both of which are dried potato commodities. These are usually given the default processing factor of 6.5. HED determined, via residue data, that the processing factors for these commodities are actually <1. Using a processing factor of 1 allows for a more conservative estimate of the acute dietary exposure and risk. Acute dietary risk estimates were 9.8% of the aPAD at the 95th percentile for the general U.S. population and 25% of the aPAD for the highest exposure group, children 1-2 years old. (HED Hot Sheet #12 states that the results of a Tier 2 acute analysis is to be reported at the 95th percentile). The results of the acute analysis indicate that the Tier 2 acute dietary risk estimates associated with the registered and HED recommended uses of fipronil do not exceed HED's level of concern (Table 16). Additional refinement by incorporating %CT information may result in even lower exposure estimates.

Table 16. Acute Aggregate Exposures to Fipronil.

Subgroups [1]	aPAD (mg/kg/day)	Exposure (mg/kg/day)	% aPAD
U.S. Population	0.025	0.002458	9.8
All infants (<1 year old)	0.025	0.003436	14
Children (1-2 years old)	0.025	0.006303	**25**
Children (3-5 years old)	0.025	0.004571	18
Children (6-12 years old)	0.025	0.002954	12
Youth (13-19 years old)	0.025	0.001889	7.6
Adults 20-49 years old.	0.025	0.001460	5.8
Females (13-49 years old)	0.025	0.001410	5.6
Adults (50+ years old)	0.025	0.001211	4.8

[1] HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys, (e.g., non-nursing infants, etc.). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (e.g., all infants, females, 13-50 years, etc.).

5.2 Short + Intermediate-Term Aggregate Risk (food + residential + drinking water)

Short + Intermediate-Term aggregate risk estimates are below HED's level of concern.

Short-term Aggregate Risk

The short-term aggregate risk assessment takes into account average exposure estimates from dietary consumption of fipronil (food and drinking water) and non-occupational exposures (pet uses). Postapplication exposures from the use on pets is considered short-term. Therefore, a short-term aggregate risk assessment was conducted, using children with combined dermal and oral exposures from pet uses as a worst case. Table 17 summarizes the results. Since the level of concern (LOC) is different for oral and dermal exposures, 300 and 100, respectively, the Aggregate Risk Index method was used to determine short-term aggregate risk. The aggregate ARI from food, water, and non-occupational exposures is 1.2. Therefore, **short-term aggregate risk estimates do not exceed HED's level of concern** (i.e. ARIs greater than or equal to 1). Adult post-application risk is considered negligible and so an aggregate risk for adults is not considered necessary.

Table 17. Aggregate Short-term

Population	food + water				oral			dermal			ARI Aggregate
	LOAEL	EXP	LOC	MOE	LOAEL	LOC	MOE	NOAEL	LOC	MOE	
All infants (< 1 year old)	0.1	0.000239	300	420	0.1	300	3300	5	100	5000	1.2

LOC=Level of Concern

MOE= NOAEL (or LOAEL)/exp

$ARI = MOE_{Calculated}/MOE_{LOC}$

$ARI_{Aggregate} = 1/((1/ARI_{food})+(1/ARI_{oral})+(1/ARI_{dermal}))$

Intermediate-Term Aggregate Risk

The intermediate-term aggregate risk assessment takes into account average exposure estimates from dietary consumption of fipronil (food and drinking water) and non-occupational exposures (turf). An intermediate-term aggregate risk assessment was conducted, using Adults 50+ with combined dermal and inhalation exposures from turf uses as a worst case. Intermediate-term risk to children is not expected to be higher than short-term risk due to the lack of inhalation exposure and a soil ingestion MOE of 1 million. Table 18 summarizes the results. Since the level of concern (LOC) is different for oral/inhalation exposures and food, 100 and 300, respectively, the Aggregate Risk Index method was used to determine intermediate-term aggregate risk. The aggregate ARI from food, water, and non-occupational exposures is 2.3 for adults. Therefore,

intermediate-term aggregate risk estimates do not exceed HED's level of concern (i.e. ARIs are greater than or equal to 1).

Table 18. Aggregate Intermediate-term

Population	food + water				dermal			inhalation			ARI Aggregate
	LOAEL	EXP	LOC	MOE	LOAEL	LOC	MOE	NOAEL	LOC	MOE	
Adults 50+	0.1	0.000101	300	990	5	100	1700	0.05	100	1500	2.3

LOC=Level of Concern

MOE= NOAEL (or LOAEL)/exp

$ARI = MOE_{Calculated}/MOE_{LOC}$

$ARI_{Aggregate} = 1/((1/ARI_{food})+(1/ARI_{oral})+(1/ARI_{inhalation}))$

5.2. Chronic Aggregate Risk (food + drinking water)

Chronic aggregate risk estimates are above HED's level of concern. A Tier 2 chronic analysis was performed using ARs from field trial data, processing factors, %CT information from the last fipronil dietary analysis (DP Barcode: D248827, S. Levy, 02/20/2001) and a new water (chronic) tolerance of 0.006909 ppm. New AR data for potato and sweet potato commodities, as well as processing factors, were provided by HED (DP Barcode: D313293, M. Sahafeyan, 8/5/2005). New projected market share data for onions, potatoes and sweet potatoes were provided by BEAD (from email, Halvorson). Processing data for wheat RACs are not available at this time; therefore the wheat, grain tolerance was used for all wheat commodities. HED also determined that existing tolerances on livestock should been maintained. The results of the chronic analysis indicate that the **Tier 2 chronic dietary risk estimates associated with the registered and HED recommended uses of fipronil exceed HED's level of concern** (Table 19).

Table 19. Chronic Aggregate Exposures to Fipronil

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.0002	0.000095	47
All Infants (< 1 year old)	0.0002	0.000239	**120**
Children 1-2 years old	0.0002	0.000156	78
Children 3-5 years old	0.0002	0.000142	71
Children 6-12 years old	0.0002	0.000094	47
Youth 13-19 years old	0.0002	0.000070	35
Adults 20-49 years old	0.0002	0.000083	42
Females 13-49 years old	0.0002	0.000081	40

Table 19. Chronic Aggregate Exposures to Fipronil			
Population Subgroup	**cPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**% cPAD**
Adults 50+ years old	0.0002	0.000101	51

6.0. DATA GAPS/LABEL CHANGES

6.1. Chemistry

For the SC formulation:

The petitioner should submit a revised Section B reflecting PBI restrictions on Regent® 4 SC label [EPA Reg. No. 7969-207] as below:

A) The appropriate PBI for root, leafy and legume vegetables is 4 months.

B) The appropriate PBI for wheat is 2 months.

C) Rotation to all other crops (except primary crops) should be prohibited.

BASF should correct the chemical name for MB46136 as: (5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile); thus, a revised section F is required.

Based on these results, the appropriate tolerances for indirect/inadvertant residues of fipronil + metabolites MB46136 and MB45950 + photodegradate MB46513 are 0.005 ppm on wheat grain, 0.02 ppm on forage, 0.03 ppm on hay and 0.03 ppm on straw. A revised Section F is required.

6.2. Toxicology

28-day inhalation toxicity study in the rat.

Note to RD: There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158 for fipronil and the hazard endpoints have been identified. However, this toxicity study in the rat is requested to further characterize the inhalation risk for use in the risk assessment of fipronil. The protocol for the existing 90-day inhalation toxicity study (OPPTS Guideline 870.3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.

6.3. Occupational/Residential Exposure

The proposed Regent 4 SC label states, "Do not enter or allow worker entry into treated areas during the REI of 0 hours." **This language is not supported by the Worker Protection Standard regulation.**

For Regent 4 SC, due to the nature of the use pattern (soil incorporation), the REI is based on the acute toxicity of the active ingredient, fipronil. Since fipronil falls into Acute Toxicity Category III for dermal and eye irritation and Category IV for skin irritation, **the REI shall be 12 hours. RD should ensure that the proper REI appear on Regent 4 SC labels.**

The following language should be stated on the Regent 4 SC label in the box "Agricultural Use Directions:"

> *Exception: if the product is soil-injected or soil-incorporated, the Worker Protection Standard, under certain circumstances, allows workers to enter the treated areas without restriction if there will be no contact with anything that has been treated.*

The proposed BES 100 Insecticide label carries an 8 hour REI.

7.0. ATTACHMENTS

Attachment 1: Fipronil: Third Reevaluation - Report of the HIARC (available electronically).
Attachment 2: MB46513, Photodegradate of Fipronil: Reevaluation - Report of the HIARC (available electronically).
Attachment 3: FQPA SFC Report (available electronically).
Attachment 4: IRLS Form.
Attachment 5: Dietary Exposure Analyses (available electronically).

B.Hanson:284:CM#2:(703)305-6891:7509C:TRB

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(available electronically).

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ATTACHMENT 4. IRLS SHEET

Chemical Name:	Common Name:	☒ Proposed tolerance ☐ Reevaluated tolerance ☐ Other	Date:
5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(1R,S)-(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile	Fipronil		7/27/05

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above ☐ No Codex proposal step 6 or above for the crops requested	Petition Number: 2E6490, 5F6948 DP #: 318283 Other Identifier:
Residue definition: N/A	Reviewer/Branch: M. Sahafeyan /RAB1
	Residue definition: parent + 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)]-1H-pyrazole-3-carbonitrile; 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile; and 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)thio]-1H-pyrazole-3-carbonitrile

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Potato/Sweet Potato (Crop Subgroup 1C)	0.03
		Potato Wet Peel	0.10
		Onion, dry-bulb	0.03
		Wheat, grain	0.04
		Wheat, forage	0.04
		Wheat, hay	0.06
		Wheat, straw	0.06

Limits for Canada	Limits for Mexico
X No Limits ☐ No Limits for the crops requested	☐ No Limits ☐ No Limits for the crops requested
Residue definition: N/A	Residue definition: fipronil

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
		cottonseed	0.010

Notes/Special Instructions: S. Funk, 8/3/2005

Attachment 5: Dietary Exposure Analyses (available electronically).

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R121482

Chemical: Fipronil

PC Code: 129121
HED File Code: 14000 Risk Reviews
Memo Date: 2/1/2006
File ID: DPD324269
Accession #: 412-06-0013

HED Records Reference Center
2/27/2006